The clinical and cost-effectiveness of anakinra for the treatment of rheumatoid arthritis in adults

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The clinical and cost-effectiveness of anakinra for the treatment of rheumatoid arthritis in adults

Produced by West Midlands Health Technology Assessment Collaboration

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About 'home unit'
The West Midlands Health Technology Assessment Collaboration (WMHTAC) is an organisation involving several universities and academic groups who collaboratively produce health technology assessments and systematic reviews. Most of our members are based in the Department of Public Health & Epidemiology, University of Birmingham, however other members are drawn from a wide field of expertise including economists and mathematical modellers from the Health Economics Facility, University of Birmingham, and pharmacists and methodologists from the Department of Medicines Management, Keele University and the Centre of Evidence-Based Pharmacotherapy, Aston University.

WMHTAC produce systematic reviews and economic evaluations for NHS R&D HTA programme (NCCHTA), the National Institute for Clinical Excellence (NICE), and for the health service in the West Midlands. WMHTAC also undertakes methodological research on health technology assessment, and provides training in systematic reviews and health technology assessment.

Contributions of authors
Wendy Clark carried out the searches, applied the inclusion and exclusion criteria, and extracted data. She wrote parts of the introduction and background, the narrative on key studies, conducted the meta–analyses wrote the discussion, responded to peer-review and edited the report.

Dr Paresh Jobanputra wrote the majority of the introduction and background, carried out data extraction, developed the cost and utility inputs for the Birmingham Rheumatoid Arthritis Model (BRAM), responded to peer-review and edited the report.

Dr Pelham Barton constructed and analysed the Birmingham Rheumatoid Arthritis Model (BRAM), appraised the industry models, responded to peer-review and edited the report.

Dr Amanda Burls supervised the project, conducted the analysis of study 0757, assisted in the economic analysis, responded to peer-review and edited the report.

Conflicts of interest
None of the members of the review team have any conflicts of interest. Dr P Jobanputra is a member of the British Society for Rheumatology. He was not involved in formulating guidelines for the use of Anakinra proposed by the BSR nor was he involved in any other submissions to NICE.

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None of the authors have or have had any pecuniary relationship with Amgen, specific or non-specific.

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Please note:

A small amount of information was submitted to the National Institute for Clinical Excellence in confidence and has been removed from this version of the report. However, it should be noted that the Institute's Appraisal Committee had access to the full report to draw up their guidance.

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Summary

Description of technology

This report reviews the evidence of the clinical and cost-effectiveness of anakinra, an interleukin-1 receptor antagonist (IL-1Ra), for the treatment of rheumatoid arthritis in adults. Anakinra is licensed in Europe for use in combination with methotrexate, for patients with an inadequate response to methotrexate alone.

Anakinra acts in the same way as naturally occurring IL-1Ra, transiently binding to the IL-1 receptor, augmenting the natural regulation of the pro-inflammatory effects of IL-1.

Epidemiology and background

RA is a chronic illness characterised by inflammation of the synovial tissues in joints, which can lead to joint destruction. Key aims of treatment include:

- To control symptoms of joint pain and inflammation
- To minimise loss of function and to maintain or improve quality of life
- To reduce the risk of joint damage and disability
- To treat extra-articular complications of RA
- To have well-informed and satisfied patients and carers

RA affects around 0.5% to 1% of the population with approximately 421,330 patients affected in England & Wales. Prevalence increases with age so that prevalence at age 65 is six times the prevalence at age 25. Peak age of onset is in the sixth decade and RA is more common in women by a ratio of 2.5 to 1.

Corticosteroids, NSAIDs and analgesics are used to control symptoms, but early use of DMARDs is key, with the aim of slowing disease progression. There are approximately 8 DMARDs currently in common use in the UK. Variable effectiveness or loss of effectiveness over time, and toxicity hampers their use, with low continuation rates seen over time. New DMARDs are therefore of great importance. Several new agents have appeared in recent years including the biologic modifiers the TNF inhibitors, infliximab and etanercept.

Number and quality of studies, and direction of evidence

Five randomised controlled trials of anakinra in adult patients with RA, involving a total of 2,905 patients, of whom 2,146 received anakinra, were identified. All compared anakinra to placebo and all but one presented outcome data at 24 weeks. In three trials anakinra was administered in combination with methotrexate/other DMARDs and in two as monotherapy. Only two trials evaluated the licensed dose of 100mg daily.

All five trials were identified as high quality.

Summary of benefits

The results of the clinical trials are consistent with clinical benefit (compared to placebo) as measured by ACR composite response rate at 6 months. Variation in response rate was seen across the trials which is likely to be a reflection of size of the trials and the wide range of doses evaluated. Consistent benefit was seen at the higher dose evaluated (NNT to achieve an ACR20 response of 7 [95%CI 5 to 11] at licensed dose). Benefit was evident with both monotherapy and when used in combination with methotrexate.

Data on the efficacy endpoints evaluated in a large pragmatic safety study have not been made available. This is of concern. Given the nature and scale of this study such data has the potential to alter the overall findings of this review. In the absence of data we made an educated guess about the result of trial 0757. Assuming that this trial failed to reach conventional levels of statistical significance with a p-value of treatment difference of the order of $p< 0.1$ to $p<0.2$, we derived an estimate of effectiveness for trial 0757. The derived estimate has been combined with the data from the earlier trials, using a random effects model, to give our best estimate about anakinra's effectiveness for ACR 20 response: RR 1.43 (95% CI 1.16 to 1.76), RD 0.11 (95% CI 0.04 to 0.18), NNT 9 (95% CI 6 to 25)

Anakinra can be considered modestly effective in the treatment of RA based on ACR response. Reduction in HAQ scores, a measure of disability, were small. Robust data on radiologically assessed joint damage is not currently available. No conclusion can therefore be made on the effect of treatment on disease progression.

Direct comparisons with other biologic modifiers are not available. Adjusted indirect comparison suggests that anakinra may be significantly less effective at relieving the clinical signs and symptoms of RA, as measured by the ACR response criteria, than TNF inhibitors all used in combination with methotrexate. Such indirect results should of course be interpreted with caution but can be useful in guiding clinical practice in the absence of direct comparisons between agents.

Anakinra treatment was associated with a high incidence of injection site reactions. Serious adverse events were infrequent, but longer term follow up is required.

Economic Evaluation

Existing economic evaluations

- No fully published economic evaluations of anakinra in patients with RA were identified. Two abstract reports presented limited data.

Commentary on submitted model

- This is a Markov model with a six month cycle time
- There are problems associated with the structure of this model which makes its conclusion, that the ICER for anakinra is £16,545/QALY, unreliable

Summary of the economic analysis

The Birmingham Rheumatoid Arthritis Model (BRAM) was used to compare DMARD sequences of drugs, chosen to reflect current clinical practice, with and without the addition of anakinra at different points in the DMARD sequence.
The BRAM gives a base-case estimate of the ICER of anakinra of between £106,000/QALY to £604,000/QALY.

This model uses data from public domain trial results only. These trials recruited a highly selective patient population and may well overestimate the cost-effectiveness that anakinra would achieve in an average clinic population.

In the sensitivity analyses quite substantial variations were made in key parameters and ICERs were shown to be responsive. However, ICERs did not drop below £50,000/QALY in any univariate sensitivity analysis.

The BRAM produces an ICER for anakinra substantially higher than those for infliximab and etanercept. However, patients may respond to anakinra when they have not responded to other biologics, as these agents have a different mechanism of action. Thus anakinra may produce a clinically significant and important improvement in some patients that they could not otherwise have achieved.

Need for further research

- Current clinical trials with anakinra are of limited duration. RCTs are required to evaluate the efficacy, safety and cost of anakinra over the longer term in patients with such a chronic disease.
- Comparative trials of anakinra with other DMARDs and biologic modifiers are required to identify the comparative efficacy of these drugs and to guide clinical practice to optimise patient care.
- Trials are required to assess the role of anakinra in the treatment of patients who have failed to achieve a benefit whilst taking infliximab or etanercept.
- Further research is required to assess the impact of DMARDs and anakinra on joint replacement, mortality and quality of life. Also, continued pharmacovigilance and analysis of potential adverse effects of new and old DMARDs is essential.
- Optimal treatment of RA in the future may require combinations of therapeutic compounds that inhibit different mediators. Controlled clinical trials of combination therapy with two anti-cytokines is required to inform clinical practice, before such an approach is widely adopted.
- Suggestions that newer biologic therapies reduce radiographic damage without necessarily improving clinical outcomes need to be confirmed if treatments in the absence of a clinical response are to be justified.
- Further research is needed to improve the utility of radiographic outcomes in clinical trials of RA either by building on existing efforts with plain radiographs or through the use of newer imaging methods.

ABBREVIATIONS

ACR	American College for Rheumatology
ADRs	Adverse drug reactions
ANC	Absolute neutrophil count
ARA	American Rheumatism Association
AZA	azathioprine
BCP	biochemical profile
BP	blood pressure
BRAM	Birmingham Rheumatoid Arthritis Model
BSR	British Society for Rheumatology
CRP	C-reactive protein
CXR	chest X-ray
CyA	ciclosporin A
DAS	Disease Activity Score
DCARD	disease control with anti-rheumatic drug
DMARD	disease modifying anti-rheumatic drug
D-Pen	penicillamine
EMS	early morning stiffness
ERAS	Early Rheumatoid Arthritis Study
ESR	erythrocyte sedimentation rate
EULAR	European League Against Rheumatism
FBC	full blood count
FDA	Food and Drug Administration
GP	general practitioner
GST	injectable gold
HAQ	Health Assessment Questionnaire
HCQ	hydroxychloroquine
HLA	human leukocyte antigen
HTA	health technology assessment
ICER	incremental cost-effectiveness ratio
IgA	immunoglobulin A class
IgG1	immunoglobulin G (class I)
IgM	immunoglobulin M
Igs	immunoglobulins
IL-1	interleukin-1
IL-2	interleukin-2
IL-6	interleukin-6
IL-8	interleukin-8
IL-10	interleukin-10
IL-1β	interleukin-1 beta
IL-1Ra	interleukin-1 receptor antagonist
ISR	injection site reaction
i.v.	intravenous
i.m.	intramuscular
LEF	leflunomide
LFT	liver function tests
LOCF	last observation carried forward

LOE	lack of efficacy
MCP	metacarpophalangeal joint
MCV	mean red blood cell volume
MeSH	medical subject heading
MRI	magnetic resonance imaging
MTP	metatarsophalangeal joint
MTX	methotrexate
NA	not applicable
NICE	National Institute for Clinical Excellence
NNT	number needed to treat
NOAR	Norfolk Arthritis Register
NSAIDs	non-steroidal anti-inflammatory drugs
OT	occupational therapy
PIP	proximal interphalangeal joint
PSS	personal social services
QALY	quality-adjusted life-year
QoL	quality of life
QSE	quasi-standard error
RA	rheumatoid arthritis
RCT	randomised controlled trial
RD	risk difference
RF	rheumatoid factor
RR	relative risk
SAE	Severe adverse event (see definition below)
s.c.	sub-cutaneous
SD	standard deviation
SEM	standard error of mean
SF-36	Short Form with 36 items
SIGN	Scottish Intercollegiate Guidelines Network
SLE	systemic lupus erythematosus
SJC	swollen joint count
SMARD	symptom modifying anti-rheumatic drug
SMD	standardised mean difference
SMR	standardised mortality ratio
SPC	summary of product characteristics
SSZ	sulfasalazine
TBD	to be determined
TJC	tender joint count
U&E	urea and electrolytes
URTI	upper respiratory tract infection
UTI	urinary tract infection
VAS	visual analogue scale
WMD	weighted mean difference

DEFINITIONS OF TERMS

Severe Adverse Events (SAE)
An event suggesting significant hazard including fatal or life-threatening events, those requiring or prolonging hospitalisation, events resulting in persistent or significant disability/incapacity, congenital abnormality or birth defect.

1 AIM OF THE REVIEW

- To provide a background on rheumatoid arthritis including epidemiology, current therapeutic options, and impact of disease on individuals and health services.
- To conduct a systematic review and meta-analysis of the clinical benefits and hazards of using anakinra in rheumatoid arthritis.
- To review the economic evidence about the cost-effectiveness of anakinra compared with other treatment options.
- To describe other agents being developed for the treatment of RA, and outline areas for research.

2 BACKGROUND

2.1 Description of underlying health problem

2.1.1 Clinical features of rheumatoid arthritis

Rheumatoid arthritis (RA) is a systemic inflammatory disorder that mainly affects synovial joints. The pathological hallmarks of RA are an inflammatory reaction, increased cellularity of synovial tissue and joint damage. RA is characterised by pain, swelling and stiffness of synovial joints. These symptoms are often worse in the morning and after periods of inactivity. RA may also affect other organ systems with a potential for severe disability and life-threatening complications. For example patients may develop lymph node enlargement, anaemia, a raised platelet count, pulmonary disease such as pleurisy or interstitial lung disease, pericarditis, vascular inflammation (vasculitis), skin nodules, and eye diseases such as reduced tear production or inflammation. Patients commonly also experience lethargy and occasionally experience weight loss, and fever.

The severity of disease can be very variable. In a community cohort 18% of RA patients were in 'remission off treatment' after 3 years follow-up. By contrast 47% of patients were classified as having moderate disability as rated by a Health Assessment Questionnaire (HAQ) score of greater than 1.0, and 25% of patients have a joint replaced within 22 years of disease onset.[1,2] (For details of the HAQ see Appendix 1, page 87). Symptoms of RA may have a rapid onset (overnight in some cases) or evolve over weeks, months or years.[3]
Common patterns of disease are:

1. Disease of small or medium joints particularly metacarpophalangeal (MCP) and proximal interphalangeal (PIP) joints of the hands, metatarsophalangeal joints of the feet, wrists and ankles. There may also be variable large joint disease.
2. Predominantly large joint disease.
3. Disease involving only a few joints, or sometimes only one joint.
4. Less common presentations: pain and stiffness affecting the shoulder and hip girdles (polymyalgic presentation); systemic symptoms such as weight loss and joint pain without a true arthritis; intermittent short-lived attacks of arthritis ('palindromic rheumatism').

The clinical course of RA and the responses of any one individual to disease are also variable. Pain and disability of early RA is linked to disease severity and to measures of psychological distress.[4] The course of RA may follow three broad patterns: progressive

disease with significant functional limitations in time, intermittent disease (where disease is punctuated by partial, or complete, remissions), and disease with long clinical remissions.[5]

2.1.2 Diagnosis of rheumatoid arthritis

Rheumatoid arthritis is diagnosed from a constellation of clinical and laboratory or radiographic abnormalities. Diagnosis may be obvious in some but in others it may be more difficult and require a period of clinical observation. Classification criteria for RA have been devised to aid research. Most contemporary research studies of RA include patients who satisfy such criteria. The most recent criteria, formulated by the American Rheumatism Association (ARA) in 1987, are shown in Table 1 (page 15).[6] These criteria were derived from a group of typical patients who had been diagnosed with RA and had well-established disease. They have limited utility in routine practice and most clinicians diagnose RA without formal reference to such criteria, with many patients not meeting formal criteria at least early in their disease.[7;8] Criteria were also developed as an algorithm. These are more readily met in clinical practice.[9]

2.1.3 Radiographic features of rheumatoid arthritis

Early in disease radiographs may show soft tissue swelling and reduced bone density around affected joints. Later there may be evidence of joint damage such as joint erosions. 'Erosion' refers to focal loss of bone and cartilage that occurs near the joint margin. More diffuse loss of cartilage results in a reduced joint space. As joint damage progresses joint deformity or instability may occur and at a late stage bony ankylosis or fusion may occur. With advanced joint damage surgical intervention such as joint replacement arthroplasty, joint fusion or osteotomy may be necessary. At an earlier stage other surgeries such as removal of synovial tissues (synovectomy) or soft tissue procedures such as tendon release or repair may be necessary.

Table 1: 1987 Revised ARA Criteria for Classification of Rheumatoid Arthritis

Criteria	Definition
Morning stiffness	Morning stiffness in and around the joints lasting at least 1 hour before maximal improvement
Arthritis of three or more joints	At least 3 joint areas have simultaneously had soft tissue swelling or fluid (not bony overgrowth alone) observed by a physician. The 14 possible joint areas are (right or left): PIP, MCP, wrist, elbow, knee, ankle and MTP joints.
Arthritis of hand joints	At least one joint area swollen as above in wrist, MCP or PIP joint
Symmetrical arthritis	Simultaneous involvement of the same joint areas on both sides of the body (bilateral involvement of PIP, MCP, or MTP joints is acceptable without absolute symmetry).
Rheumatoid nodules	Subcutaneous nodules, over a bony prominence, or extensor surface or in juxta-articular regions, observed by a physician.
Serum rheumatoid factor	Demonstration of abnormal amounts of serum 'rheumatoid factor' by any method that has been positive in less than 5% of control subjects.
Radiographic changes	Radiographic changes typical of RA on postero-anterior hand and wrist radiographs, which must include erosions or unequivocal bony decalcification localised to or most marked adjacent to the involved joints (osteoarthritis changes alone do not qualify).
A patient is said to have RA if he or she satisfies at least 4 of the above 7 criteria. Criteria 1 through 4 must be present for at least 6 weeks. Patients with two clinical diagnoses are not excluded.	

Adapted from Arnett et al (1988)[6]

2.1.4 Epidemiology

RA is the most common form of inflammatory arthritis. It affects around 0.5% to 1% of the population. Recent estimates from England and Wales show an annual incidence of 31 per 100,000 women and 13 per 100,000 men and a prevalence of 1.2% in women and 0.4% in men.[10] Therefore there are approximately 476,170, patients with RA in the UK, and 421,330 (309,890 women and 111,440 men) in England & Wales (population 52,041,916).[11] This means that an average Health Authority with a population of half a million has 4,000 patients with RA. The incidence of RA in the UK appears to have declined in recent decades.[12] Prevalence increases with age so that prevalence at age 65 is six times the prevalence at age 25. Peak age of onset is in the sixth decade and RA is more common in women by a ratio of 2.5 to 1.[13]

2.1.5 Aetiology

No single cause of RA has been identified. It appears to be a multi-factorial disease in which there are important genetic and environmental influences:

- Genetic influence is estimated at 50 to 60%.[14] Much of this contribution comes from the human leukocyte antigen (HLA) region of chromosome 6, particularly HLA-DR4. HLA plays a key role in immune function and regulation. The only known function of DR is in presentation of peptides to T cells for mounting an immune response to particular antigens. The occurrence of RA in both monozygotic twins is 12%-15%.[12;13] A family history of RA gives an individual a risk ratio of 1.6 compared with the expected population rate.[15]

- Infectious agents have been suspected as causal agents but without any conclusive or convincing evidence.[16;17]
- Lifestyle factors such as diet, occupation, or smoking are not causally linked to RA.
- Sex hormones are implicated since there is an increased incidence in women and, in general, improvement during pregnancy.[12]
- Rheumatoid factor, an autoimmune response to IgG is a key feature of RA. High levels are relatively specific for RA but rheumatoid factor may also occur in other chronic diseases and is absent in around 30% of patients with established RA.

2.1.6 Pathology

The pathological hallmark of RA is synovial hyperplasia and an inflammatory reaction of synovial tissues. This is accompanied by an inflammatory exudate into the joint cavity. Synovial fluid in RA is highly cellular and contains predominantly polymorphonuclear cells with lesser numbers of T cells and macrophages. In disease, the synovial lining layer is increased to up to a 10-cell layer thickness. There are more blood vessels and populations of activated cells such as fibroblasts, T lymphocytes, plasma cells (antibody producing cells) and cells resembling macrophages.

Cytokines, small peptides that mediate signals between cells, primarily in a localised environment, and their receptors are produced in greater quantities in inflamed synovial tissues. Erosion, or destruction, of cartilage and bone commonly occurs where synovial tissue meets cartilage and bone. This occurs through the combined actions of 'invasive' synovial tissue (pannus) and resident cartilage and bone cells. Erosions may be seen on X-rays and are useful in diagnosis. Erosions, and loss of cartilage in a synovial joint, are rarely reversible. Such damage therefore compromises the structure and function of a normal joint.

2.1.7 Role of cytokines in RA

Almost all biological processes involve cytokines. This includes normal development, immunity and inflammation. Cytokines are multifunctional and are highly expressed in RA tissues.[18-20] They function in a network of overlapping, synergistic, antagonistic and inhibitory activities. The net biological response appears to depend on the balance of counter-acting factors.[21] Tumour necrosis factor (TNF) and interleukin-1 (IL-1) are two of the key proinflammatory cytokines in RA. In early disease (< 6months) both cytokines are expressed in abundance.[22]

IL-1 and TNFα have both local and systemic effects in RA. Locally they enhance the migration of leukocytes from the circulation into the inflamed joint. They also contribute to the growth of new blood vessels, which characterises rheumatoid synovitis. Most importantly, IL-1 and TNFα are key mediators of the tissue destruction and osteopenia seen in a rheumatoid joint.

The relationship between cytokines is complex. TNFα appears to regulate production of a variety of pro-inflammatory agents including IL-1.[20] IL-1 itself can induce expression of TNFα and also uniquely up-regulate its own expression.[22] IL-1 and TNFα have overlapping effects but IL-1 is recognised as a primary inducer of acute-phase proteins,[23] and appears to have a more important role in promoting cartilage and bone destruction.

2.1.8 Role of Interleukin-1 and interleukin-1 receptor antagonist in RA

There are three members of the IL-1 gene family: IL-1α, IL-1β and IL-1Ra. IL-1α and IL-1β are secreted by immune cells in response to infectious or inflammatory challenge. IL-1Ra (IL-1 receptor antagonist) regulates IL-1α and IL-1β activity by blocking their actions.

Each member of this family binds to two receptors, designated type 1 (IL-1RI) and type 2 (IL-1RII), that are present on a variety of cells. The binding of IL-1α and IL-1β to type 1 receptors leads to cellular signalling and biological effects. By contrast binding of IL-1α and IL-1β to the type 2 receptor (IL-1RII) does not cause cellular signalling. IL-1RII is a 'decoy' receptor that functions by scavenging IL-1α and IL-1β. IL-1Ra competes with IL-1α and IL-1β for binding to type 1 receptors. Binding of IL-1Ra to IL-1R1 does not lead to cellular signalling.

Both receptors (IL-1RI and IL-1RII) may be cleaved from cell surfaces and circulate as soluble proteins (sIL-1RI and sIL-1RII). Soluble receptors may also bind to all members of the IL-1 family. However sIL-1RII preferentially binds to IL-1α and IL-1β, further inhibiting the activity of these cytokines. Binding of sIL-1RI to IL-1Ra reduces the amount of IL-1Ra that is available to inhibit the actions of IL-1α and IL-1β.[24 23,25,26;27]

Mice in whom the gene for IL-1Ra has been knocked-out develop either an inflammatory arthritis resembling RA or a lethal arterial inflammation.[28;29] These data support the concept that an imbalance in IL-1 regulation can lead to destructive tissue inflammation.

IL-1Ra is found in large amounts in the synovial fluid and tissues of patients with RA, but local production appears to be insufficient to effectively inhibit IL-1. Fewer than 5% of type 1 receptors need to be occupied by IL-1 in order to induce biological responses.[25] High local tissue concentrations of IL-1Ra must therefore be achieved to be physiologically inhibitory, a 10 to 1000 fold excess of IL-1Ra being required to block the effects of IL-1 in vivo.[25]

2.1.9 Goals of management

The goals of treating RA are:[30,31]

- To control symptoms of joint pain and inflammation
- To minimise loss of function and to maintain or improve quality of life
- To reduce the risk of joint damage and disability
- To treat extra-articular complications of RA
- To have well-informed and satisfied patients and carers

As with any chronic incurable disease a long-term treatment plan is required that is repeatedly re-examined in the light of clinical parameters and patient preferences.[32] Clinicians recognise that many factors need to be considered during this interaction with patients.[33] These include:

- Discussion of drug and non-drug therapeutic options. An open discussion about the benefits and risks of these options including an awareness of the hazards of untreated disease and also of rare potentially life-threatening adverse events with some drugs

- Modes of drug administration and monitoring needs to ensure safe use of particular drugs
- Assessment of psychosocial factors such as available social support, adjustment to disease, needs of dependants and effect on employment and employability
- Educational needs of patients and carers
- Co-morbidity that may influence drug use and prognosis
- Drug costs

2.1.10 Current drug therapy for rheumatoid arthritis

Conventional drug therapy for rheumatoid arthritis relies on varying combinations of the following four classes of drugs:

- Non-steroidal anti-inflammatory drugs (NSAIDs)
- Analgesics
- Corticosteroids such as prednisolone and methylprednisolone
- Disease modifying anti-rheumatic drugs (DMARDs) including sulfasalazine, methotrexate, gold preparations, penicillamine, azathioprine, hydroxychloroquine, leflunomide, ciclosporin A and biologic modifiers (e.g. TNF inhibitors)

Daily pain control and stiffness are managed by NSAIDs, low dose prednisolone (for example prednisolone 10 mg or less), analgesics or a combination of these. The risks and benefits of NSAIDs are well recognised and have been reviewed extensively elsewhere.[31;34] Corticosteroids may be given in varying doses by mouth, or as intra-articular, intramuscular or intravenous injections. They are often used as short-term treatment for acute relapses, as 'bridge therapy' or 'step down therapy' to allow rapid control of disease whilst awaiting the effects of DMARDs.[35] The benefit of corticosteroids on symptoms of RA does not appear to be sustained in randomised trials. However, in clinical practice, a significant proportion of patients are maintained on corticosteroids long-term, indicating sustained benefit for some patients.[35;36] Long-term therapy may also be justified on the grounds that low-dose prednisolone prevents joint damage.[37]

DMARDs are slow acting drugs that provide symptomatic relief and reduce the risk of progressive joint damage. Most DMARDs take several weeks or months to work. The mode of action of many DMARDs is not fully understood but many appear to act by immune suppression. For example methotrexate (MTX) and leflunomide, a newly available DMARD, are anti-metabolites.[38] Inhibitors of TNFα, etanercept and infliximab, are very effective agents in RA and are being widely used.[39]

It is generally accepted that patients with RA should be treated with DMARDs soon after diagnosis. Delayed use of DMARDs leads to worse outcomes.[31;40;41] DMARDs are usually given with NSAIDs, analgesics, corticosteroids, or a combination, at least initially. As disease control is achieved doses of other drugs may be reduced, or drugs discontinued, while maintaining therapy with DMARDs. Comparisons between DMARDs indicate that oral gold, azathioprine and hydroxychloroquine are less effective than other agents.[31;38;42] The remaining drugs appear to have comparable efficacy. A meta-analysis of treatment termination rates showed that continued drug use 5 years after starting a DMARD was 36% for methotrexate, 23% for i.m. gold, and 22% for sulfasalazine. Median time for drug use for these agents was 41 months, 24 months and 18 months respectively, underlining a key

limitation of DMARDs.[43] That is relatively short-term use, or drug survival, of a DMARD for a disease with a life-long course.

DMARDs may be discontinued because of toxicity, inadequate disease control, disease relapse, patient or physician preference, complicating co-morbidity or a combination of these.[44] DMARD toxicity varies from relatively minor adverse reactions to life-threatening events such as bone marrow suppression. Antimalarial drugs and methotrexate appear to have the most favourable risk-benefit profile.[45] Methotrexate is widely regarded as the standard against which other drugs should be judged especially because of its lower propensity for treatment termination. Effective disease control may also lead to other benefits such as reduced cardiovascular mortality.[46]

DMARDs are used in a variety of ways. Some use several agents at once in patients with severe disease ('combination therapy'), others use DMARDs in sequence and either add one DMARD to another or replace one DMARD with another in an effort to attain disease control.[47] Increasingly, combinations of DMARDs are used although evidence in favour of combining DMARDs is limited.[48-50] Preferred DMARD combinations include methotrexate combined with hydroxychloroquine or ciclosporin A. [47] Of the newer biological modifiers, infliximab is only currently licensed for use in combination with methotrexate. An analysis of sequential use of DMARDs suggests that there may be reduced likelihood of sustained therapy with each successive DMARD.[51] It appears that the prospect of prolonged therapy for a DMARD is greatest if that DMARD is the drug first used in a sequence of DMARDs.[52] The choice of initial DMARD does not seem to be relevant suggesting that failure to respond to methotrexate, or any other specific DMARD, is not a marker for a resistant form of RA.[51]

Patients whose disease is well controlled, or in remission, whilst taking DMARDs often seek to reduce their medication. Discontinuing treatment increases the risk of relapse and guidelines advocate sustained long-term therapy.[53;54] However it is not widely acknowledged that only around 60% of patients are fully compliant with DMARD therapy and that nearly a quarter are consistently non-compliant.[55]

Disease in some patients appears to be resistant to conventional approaches but there is no clear definition of 'resistant RA'. Criteria for 'refractory' RA have been proposed recently. [56] The following demands must be met, according to the criteria described:

That patients have used at least 3 DMARDs including methotrexate ($\geq$ 15 mg/week) and sulfasalazine (dose $\geq$2 g / day) for a minimum of 6 months unless there was toxicity.

- Lack of efficacy is defined by failure to improve the Disease Activity Score, (DAS), by $\geq$0.6 (discussed below)
- That patients have persistently active disease (DAS>3.7) despite therapy

2.1.1.1 Toxicity of DMARDs

The high rate for discontinuation of DMARDs is a key concern in rheumatology. In general, drug toxicity arises during the first months of therapy. After 24 months drug cessation is as likely to be a result of loss of efficacy as toxicity.[52] Treatment cessation because of toxicity is more likely with i.m. gold than with sulfasalazine or methotrexate.[43] Adverse reactions to commonly used DMARDs are listed in, Table 2, page 21.

2.1.1.2 Assessment of response to DMARDs

The ultimate goal of treating any disease is complete remission. For RA this is not usually achieved, using current criteria for remission, but very effective disease control is possible in many patients. Modern clinical trials assess the response of a patient to therapy by using a composite measure that combines several measures of disease activity (Appendix 2, page 89). The ACR definition of improvement and the disease activity score (DAS) are two of the most commonly used measures. The ACR response, for example, requires an improvement in:[57]

- Tender joint count
- Swollen joint count
- At least 3 of :
    - global disease activity assessed by observer
    - global disease activity assessed by patient
    - patient assessment of pain
    - physical disability score (e.g. HAQ)
    - acute phase response (e.g. ESR or CRP)

Response is defined as ACR20, ACR50 or ACR70 where figures refer to %age improvement of the clinical measures shown above. This creates a dichotomous outcome of responders and non-responders. Achieving an ACR20 response has been regarded as a low hurdle but in clinical practice patients who achieve this hurdle may still gain a worthwhile clinical response, especially in early RA.[58;59] The perspective of regulatory agencies in approving new drugs for RA was summarised in our review of anti-TNF therapies.[39]

Radiographic outcomes are believed by many to be the most important outcome measure in RA. A variety of schemes have been developed to assess joint damage in RA using radiographs. The most commonly used measures are the Sharp and Larsen methods and modifications of these methods (Appendix 3, page 90). Plain radiographs, however, are insensitive to change but are cheap and widely available. A majority of patients show only mild or no progression on plain radiographs over periods of 1 to 2 years.[60] In addition there are significant problems of measurement error between 2 independent observers viewing the same set of radiographs. For example the smallest detectable deterioration in the hands and feet radiographs of an individual over 12 months is estimated to be 15 Sharp units and 8 Larsen units, if 95% agreement between observers is required.[61] The group mean change in the Sharp score for anti-TNF agents over 1 or 2 years was in the range 0 to 7 Sharp units.[39] Others have reported that the median annual change in Larsen units was 6.5 units in patients with high levels of clinical disease.[62] Therefore whilst radiographic outcomes are important in RA there are obvious challenges in improving the reliability and utility of radiological outcomes for clinical trials.

Table 2: Toxicity of commonly used DMARDs

Drug	Common	Uncommon	Rare or very rare
Azathioprine	Nausea, rash, hypersensitivity, mouth ulcers	Leucopenia, infection	Lymphoma (long-term use)
Ciclosporin A	Headaches, hypertension, renal impairment, depression, nausea paraesthesia, tremor, hypertrichosis gingival hyperplasia, depression	Incipient renal failure, gout	Malignancy
Etanercept	Injection site reactions, pruritus, fever, infections, allergic reactions, autoantibody formation	Serious infections, thrombocytopenia, angioedema, urticaria	Anaemia, leucopenia, pancytopenia, aplastic anaemia, serious allergic/anaphylactic reactions, seizures, CNS demyelinating disorders, malignancy
Gold	Rash and pruritus, diarrhoea (especially oral gold), mouth ulcers, thrombocytopenia, proteinuria	IgA deficiency, reduced Igs, neutropenia, cholestatic jaundice	Marrow aplasia, pneumonitis, exfoliative dermatitis
Hydroxy-chloroquine	Nausea, diarrhoea, rash, headache, dizziness, blurred vision	Muscle weakness	Retinal toxicity
Infliximab	Infusion related reactions (dyspnoea, urticartia headache), rash, pruritus, increased sweating, dry skin, fatigue, chest pain, viral infection, respiratory tract infections, sinusitis, flushing, vertigo/dizziness, nausea, diarrhoea, abdominal pain, dyspepsia, abnormal hepatic function	Fungal and bacterial infections, autoantibodies, anaphylactic reactions, anaemia, leucopenia, neutropenia, thrombocytopenia, lymphadenopathy, conjunctivitis, cardiovascular symptoms/disease, GI symptoms, abnormal skin pigmentation, alopecia, myalgia, arthralgia, injection site reactions	CNS demyelinating disorders, pancytopenia, anaphylactic shock, opportunistic infections, malignancy
Leflunomide	Hypertension, nausea, diarrhoea, mouth ulcers, abnormal LFTs, headache, dizziness, hair loss, rash	Hypocalcaemia, taste disturbance, tendon rupture, anxiety	Severe abnormality of LFTs, Stevens-Johnson syndrome, leucopenia (<2.0), pancytopenia, agranulocytosis (very rare)
Methotrexate	Abdominal pain, nausea, diarrhoea, abnormal LFTs, neutropenia, macrocytosis, subcutaneous nodules, altered mood	Pancytopenia, pneumonitis, herpes zoster	Lymphoma, liver failure, unusual and severe infections
Penicillamine	Altered taste or loss of taste, nausea, mouth ulcers, rash or pruritus, proteinuria, thrombocytopenia (dose related)	Glomerulo-nephritis	Myasthenia, polymyositis, systemic lupus erythematosus, aplasia, neutropenia
Sulfasalazine	Nausea, rash, discoloured urine, leucopenia, fever, mouth ulcers, dizziness, oligospermia, raised MCV	Neutropenia, agranulocytosis, abnormal LFTs, reduced Igs	Pneumonitis
Data are collated from a variety of sources, primarily Denman AM.[63] The term *common* indicates occurrence in approximately 1-10% of patients; *uncommon* 0.1-1%; *rare* 0.01-0.1%; *very rare* 0.01% or less. BP = Blood pressure. MCV = mean red blood cell volume. LFTs = liver function tests. FBC = full blood count. Igs = immunoglobulins.			

Adapted from and reproduced with permission from NCCHTA[39]

2.1.11 Non-drug therapy

Management of severe RA often requires input from a multidisciplinary team of health professionals.[31;64] This includes assessment, education and advice from an occupational therapist, physiotherapist, podiatrists, specialist nurses and many others. Hospitalisation occurs less often than it used to but is still sometimes needed for those with severe disease or life-threatening complications.[65]

2.1.12 Prognosis

The impact of RA on an individual can be viewed from a variety of perspectives including employment status, economic costs to the individual or society, quality of life, physical disability, life expectancy, medical complications such as radiographic damage or the need for surgery, and so on. Understandably, factors that can predict longer term outcomes at diagnosis are of great interest to patients and doctors. In general, persistent disease activity is associated with poorer outcomes but studies show an inconsistent relationship with specific markers. This probably reflects differences in settings and in selection of patients. Inception cohorts of patients with RA provide the most robust assessment of prognosis. A few well-studied outcomes and their predictors are discussed briefly below.

- *Disability* can be difficult to predict within 5 years of diagnosis, as the functional status of individuals is labile.[66]At 5 years disability (HAQ >1) is predicted by age at symptom onset, a high disability score at presentation (i.e. disability at presentation predicts itself), rheumatoid nodules, female sex, psychological status and joint tenderness.[67-69] Accuracy of 76% is reported for a combination of these factors (excluding female sex).[67] Physical function of patients followed soon after disease onset, and defined by ACR classification for function (Appendix 4, page 91) is normal in up to 40% of patients at 5 years. Moderate or severe disability occurs in 15.4%.[68]
- *Loss of employment* is related to type of employment, and other aspects of the workplace such as pace of work, physical environment, physical function, education and psychological status.[70;71] Work disability is not necessarily linked to measures of disease activity such as tender or swollen joint count. It occurs in 40% of patients 5 or more years after diagnosis and, in as many a third, 2 years after diagnosis. Rates of work disability are substantially greater than in controls in some studies, but not all.[72] Manual workers, not surprisingly, suffer most limitations.[68]
- *Serial measures of disease activity* and severity may predict radiographic damage. Markers linked to greater radiographic damage include positive rheumatoid factor, age, disease duration and extent of disease.[73] The predictive value of such factors for erosions on X-rays approaches 80% in some studies although there is considerable variation between studies.[1] Genetic markers have been shown in some studies to predict radiographic damage, however, others suggest that this may not be the case.[74] Clinical trials of DMARDs usually measure radiographic damage in the small joints of hands and feet. The degree of small joint damage correlates with extent of large joint damage and both correlate with physical function.[75;76]
- *Major joint replacement surgery* (including hip, knee, shoulder, and elbow replacements) was required in 8% of RA patients 5 years after diagnosis.[68] With longer follow-up 25% of patients had total joint arthroplasty within 22 years of disease onset.[2] Hospitalisation for medical treatment of RA shows considerable variation between centres due to

availability of in-patient facilities.[68] However medical treatment of severe RA in hospital can lead to better outcomes up to 2-years after hospitalisation, compared with routine out-patient care.[77]

- *Mortality*, especially due to cardiovascular disease, may be increased in RA. Studies of inception cohorts (defined as those with disease duration of less than 2 years) show a standardised mortality ratio (SMR) of between 0.87 and 1.38 (mean 1.22). Skin nodules, greater physical disability rheumatoid factor and treatment with steroids were associated with increased mortality.[70;78] Deaths from infection, lymphoma or leukaemia, and deaths related to the digestive system appear to occur in greater than expected proportions. The death rate at 5 years in a large British cohort of patients seen in hospital was 10.7%, whereas the rate for an inception cohort of primary care patients with RA was 13% after median follow-up of 6.9 years.[68;79]

2.1.13 Burden of illness

RA is associated with a substantial economic burden in some studies. Medication costs account for between 8 and 24% of medical costs, physician visits 8 to 21% and hospitalisation 17 to 88%. It is unclear whether indirect costs exceed direct medical costs but patients and families, rather than health care services, incur a majority of the economic costs early in disease.[80] Mean annual direct and indirect costs, for the year 1996, are reported at £3,575 and £3,638 per patient respectively.[81] Inevitably, in a disease characterised by lifelong pain, discomfort and physical impairment, the burden on individuals and families is increased. Economic disadvantage, for example because of work disability, or limited access to resources, such as aids and appliances, can have a substantial impact on the ability of an individual to function.

2.2 Current service provision

Most patients with RA are referred to hospital services but up to a quarter of patients with early inflammatory arthritis (not necessarily RA) are managed in primary care without specialist referral.[1] Joint pain is the leading reason for referral to hospital outpatient services with an annual rate of referral exceeding 40 per 1000 population.[82] The BSR and other organisations recognise a significant shortfall in rheumatology service provision (estimated at approx 300 whole-time Consultant Rheumatologists in the UK).[83;84] Prolonged waiting times for patients to be seen in hospitals, and opinions of general practitioners and patient groups, provide support for the view that rheumatology provision is insufficient.[85;86]

The majority of patients followed up in a hospital rheumatology department have RA or another type of inflammatory arthritis or connective tissue disease. A proportion of such patients may also require in-patient treatment. There are considerable variations in in-patient facilities for patients with rheumatic disease. This may account for variations in hospitalisation rates seen for RA.[83]

2.3 Description of the new intervention

2.3.1 Identification of patients and criteria for treatment

The limitations of current therapies for RA were described earlier. These limitations provide a context in which new treatments for RA should be viewed. Rigid criteria for use of any specific treatment in any one individual are inappropriate.[87;88] This is especially true for RA where, in addition to considering a patient's perspective, significant co-morbidity is likely to influence therapeutic choices.

Anakinra is only licensed in Europe for use in combination with methotrexate in those patients who have not responded sufficiently to methotrexate alone. A BSR committee has issued guidelines on the appropriate use of anakinra in RA.[89] The guidance is similar to that issued on the use of etanercept and infliximab in RA.[90] It is recommended that anakinra should only be used if the following criteria are met:

- Patients satisfy the 1987 ACR classification criteria for RA.
- Patients have highly active RA based on a DAS score of >5.1 (using DAS28, Appendix 2, page 89).
- Patients must have failed treatment with methotrexate and at least one other DMARD (from a list including i.m. gold, hydroxychloroquine, sulfasalazine, penicillamine, azathioprine, methotrexate, and leflunomide). Treatment with each DMARD should be for at least 6 months. A 'standard target dose' for a minimum of 2 months is stipulated unless toxicity requires discontinuation.
- Clinicians must register treated patients, with consent, in a central registry and provide data on drug dose, outcome and toxicity on a six-monthly basis.[91]

The BSR biologics registry is a prospective cohort study designed to compare the risk, over 5 years, of developing malignancy, lymphoproliferative malignancy, infection requiring hospitalisation, serious co-morbidity and death in two cohorts. The first cohort is a group of patients with rheumatic disorders newly exposed to a biologic drug. The comparison cohort is a group of patients with similar disease characteristics newly exposed to other non-biologic drugs. It is proposed that patients are monitored for at least 5 years and the goal is to recruit all patients treated with anti-TNF agents and anakinra. All UK hospitals are obliged to collect data on patients treated with anti-TNF agents[92] and 7 centres across the UK are recruiting the comparison cohort. The BSR and the manufacturers of etanercept, infliximab and anakinra have funded the study. Physicians contributing patient data do not receive support or reimbursement for data gathering. It seems likely that smaller units and those with less support from professions allied to medicine will have difficulty meeting the demands of the patient registry. It is unclear how complete participation can be ensured by NICE and BSR guidance nor is it apparent how standards for data recording are maintained and audited. All data collected in the registry are owned by the BSR. [93] (personal communication Kath Watson, BSRBR Study Co-ordinator, October 2002)

2.3.2 Description of the technology

Anakinra (TN Kineret®) is a recombinant, non-glycosylated form of human IL-1Ra with a single methionine residue added at the amino terminus.[94;95] It is the first biologic agent of this

type designed specifically to modify the biological response of IL-1. Amgen launched it in the UK in April 2002. It has been available in the US since November 2001.

Anakinra is administered by the patient, or carer, as a single daily subcutaneous injection. It should be administered at approximately the same time each day, with rotation of the injection site. It is supplied in pre-filled syringes containing the recommended fixed daily dose of 100mg. Pre-filled syringes of anakinra need to stored in a refrigerator (2-8^{0}C) and protected from light. Each syringe should be allowed to reach room temperature before it is administered. Anakinra pre-filled syringes should not be removed from a refrigerator for more than a single period of 12 hours (at temperatures up to 25^{0}C).

Training may be needed for administration of injections and in some cases injections may have to be administered by a healthcare professional. Patients need access to a refrigerator for storage of syringes and a sharps bin for disposal of used syringes. No other equipment is required.

The bioavailability of anakinra was 95% after a 70mg s.c. injection in healthy volunteers.[96] Peak plasma concentrations are seen within 3 to 7 hours in patients with RA. Anakinra is excreted in the urine, less than 10% unchanged, with a terminal half-life of about 6 hours. The site of metabolism is not known. Absorption of anakinra is the rate-limiting factor for clearance of the drug from plasma following s.c. injection.[97] Accumulation of anakinra does not occur after daily s.c. injections (of up to 2 mg/kg/day) for 24 weeks in RA. Plasma clearance of the drug is reduced by 70-75% in patients with severe or end stage renal disease.[94] Use in such patients is contra-indicated.[96]

Anakinra acts in the same way as naturally occurring IL-1Ra, transiently binding to the IL-1 receptor, augmenting the natural regulation of IL-1.

Anakinra is licensed in Europe 'for the treatment of the signs and symptoms of RA in combination with methotrexate, in patients with an inadequate response to methotrexate alone'.[96] The summary of product characteristics further recommends that 'treatment should be initiated and supervised by specialist physicians experienced in the treatment and diagnosis of RA.'[96] Anakinra is not recommended for use in children and adolescents under 18 years of age.

The European licence is more restrictive than the US licence which allows use 'for the reduction in signs and symptoms of moderately to severely active rheumatoid arthritis, in patients 18 years of age and older who have failed 1 or more disease modifying antirheumatic drug.' Prescribers are advised not to use anakinra in combination with TNF inhibitors.[98]

Anakinra is contra-indicated in patients with severe renal impairment and in those with hypersensitivity to the active substance, any of the excipients or to *E. coli* derived proteins. Anakinra is not recommended for use in patients with neutropenia, those with pre-existing malignancies, pregnant or breast feeding women.[96] Women of childbearing potential are advised to use effective contraception during treatment. Caution is advised in moderate renal impairment and in those with a history of recurring infections or with underlying conditions that may pre-dispose them to infections.[96] It is recommended that neutrophil counts are assessed prior to initiating anakinra treatment, monthly during the first 6 months of treatment

and quarterly thereafter. If neutropenia develops anakinra should be discontinued and neutrophil counts monitored closely.[96]

2.3.3 Degree of Diffusion

Currently data on the usage of anakinra in the NHS is limited. Amgen were unwilling to provide data on the use of anakinra in the UK since they viewed this as commercially sensitive. CONFIDENTIAL INFORMATION REMOVED.

2.3.4 Anticipated costs

The acquisition cost of one year's treatment with anakinra (100mg daily by s.c. injection) is £7471.[99] Anakinra is currently being supplied by one of two routes both of which incur additional expense: Directly by Hospital Trusts which incurs additional cost of 17.5% or by a home care company at an additional cost of 8% of the drug acquisition cost.

Additional costs associated with supervision, training, safety and efficacy monitoring, and collection of data for the BSR registry also need to be taken into account.

It is not possible to give any reliable estimate of how many RA patients are likely to be eligible for anakinra since anti-TNF agents are only now being widely used in the UK. If we assume that 30% of patients do not respond to anti-TNF agents (based on clinical trials of anti-TNF agents), and, if we assume that 10% of RA patients known to hospital departments are eligible for anti-TNF, then 3% of RA patients might be eligible for anakinra (9480 patients in England and Wales currently).[39]

3 EFFECTIVENESS

3.1 Methods for reviewing effectiveness

3.1.1 Search Strategy

The following electronic bibliographic databases were searched with a stop date of 1st November 2002:

Cochrane Library, Medline, Embase, Science Citation Index (SCI), National Research Register (NRR), NHS Database of Reviews of Effectiveness (DARE), Index to Scientific and Technical Proceedings (ISTP), NHS Economic Evaluation Database (NHS EED), Health Economic Evaluation Database (HEED).

Search terms included the text words: anakinra; kineret; interleukin-1 receptor antagonist; IL-1ra; rhu-IL-1Ra; and the index terms; arthritis, rheumatoid; receptors, interleukin-1; interleukin-1.

Studies were limited to humans. No language, date or age restrictions were applied. A meta-search engine was used to search the Internet, and links followed up. Proceedings from the American College of Rheumatology and European Congress of Rheumatology meetings were searched electronically for the years 2001 and 2002.

Scrip, FDA submissions for new drug applications, EMEA reports and the pharmaceutical company submission to the National Institute for Clinical Excellence (NICE) were hand searched. The reference lists of identified publications were reviewed to identify any additional studies and/or citations.

3.1.2 Inclusion and exclusion criteria

Two reviewers independently applied the following inclusion/exclusion criteria to all potential studies. Disagreements were resolved by discussion, referring to a third party when necessary. Reviewers were not blinded to any features of the report including authorship however inclusion/exclusion decisions were made prior to detailed scrutiny of the results.

3.1.2.1 Inclusion criteria

The criteria for inclusion related to the population, intervention and comparator considered and the publication status of the report were applicable to both the clinical effectiveness and cost-effectiveness parts of the review.

Population	Adults aged 18 years and above with rheumatoid arthritis
Intervention:	Anakinra (Kineret®) alone or in combination with other drugs
Comparator:	Placebo, or other drug treatments for RA
Publication	All data to be included irrespective of publication status.

Studies were included in the final analysis of the review if they met the above criteria and the additional criteria for study design and outcomes as specified below for the clinical and cost-effectiveness parts of the review.

Clinical effectiveness review

Study design: Randomised or quasi-randomised controlled trials

Outcomes: To include: mortality, morbidity (e.g. disability/mobility, disease progression, joint damage, pain, adverse events), response rates and quality of life.

Cost-effectiveness review

Study design: Economic evaluation studies: cost analysis, cost-effectiveness, cost-utility and cost-benefit studies. Existing health economic reviews were also assessed.

Outcomes: To include: quality of life, costs, and incremental cost-effectiveness ratio.

3.1.2.2 Exclusion criteria

- Trials only recruiting children with juvenile idiopathic arthritis.
- Trials with no comparator arm.
- Trials which were not randomised. *(clinical effectiveness part of review only)*
- Articles reporting solely on laboratory measures aimed at investigating disease or treatment mechanisms.

3.1.3 Data extraction strategy

Two reviewers independently extracted data using pre-designed data extraction forms. Disagreements were resolved by discussion. Data from studies with multiple publications were extracted and reported as a single study.

Clinical effectiveness review

The following data were extracted:

- Details of the study population and baseline characteristics of the intervention and control groups, with particular reference to disease characteristics and previous treatment history.
- Details of the intervention, such as dose, mode of administration, frequency of administration and duration of treatment
- Details of completion rates across the groups, reasons for withdrawal, loss to follow up.
- Details of individual outcomes measured such as:
  - Changes in disease activity e.g. ACR improvement criteria, swollen joint count, pain, joint space narrowing and erosion.
- Changes in quality of life
- Adverse events reported

Results were extracted, where possible for the intention to treat population, as raw numbers, plus any summary measures with standard deviations, confidence intervals and p-values where given.

Cost-effectiveness review
The following data were extracted:

- Details of the study characteristics, including type of economic analysis, intervention and comparator, perspective, time frame, modelling used.
- Details of the data used to populate the evaluation and the key assumptions made such as effectiveness data, cost data, health state valuations, discounting rate.
- Details of the results and sensitivity analysis

3.1.4 Quality assessment strategy

Two reviewers undertook quality assessments independently, using a structured approach. Disagreements were resolved by discussion, with reference to a third party where necessary.

Clinical effectiveness review
The validity of included studies were assessed by looking at the method of randomisation, the concealment of allocation, the comparability of baseline characteristics between the different arms, blinding, withdrawals and losses to follow-up for each patient group. Based on these criteria a Jadad score was calculated. (The Jadad score ranges from 0 to 5, with a score of 5 representing trials of highest quality).

Cost-effectiveness review
The criteria of Drummond et al served as an a priori standard for the assessment of economic evaluations.[100] These evaluate the study question, selection of alternatives, form of evaluation, effectiveness data, costs, benefit measurement and valuation, decision modelling, discounting, allowance for uncertainty and presentation of results.

3.2 Results

3.2.1 Quantity and quality of research available

Sensitive rather than specific search strategies were used. The considerable interest in the potential role of biological therapies in the management of RA, particularly following the positive research data on anti-TNF therapy has generated a large number of publications. Identified reports included many reviews, news articles, observational studies and studies investigating IL-1 related disease mechanisms as well as a small number of clinical trials of IL-1Ra therapy. Results of Medline and Embase Searches are shown in Appendix 5, page 92.

3.2.2 Identified studies, inclusions and exclusions

Fifty eight publications that potentially reported relevant trials were identified; 13 published reports, 45 abstracts. All were identified from searches of electronic databases.

A number of duplicate publications were identified which included; abstracts for trials subsequently published in full, abstracts on the same data presented at more than one meeting, full reports of the same trial published in more than one journal. Where identical data were presented in different publications then, if available, the fully published report was included. Where there were duplicate abstracts the most recent report was included. In the case of duplicates of fully reported trials the original report was included.

In other cases several abstracts and full papers presented sub-sets of data or details of a specific outcome. These were included if pertinent outcome data, not found in other sources, were presented.

Efficacy data from the open-label extension phase of blinded studies, or studies that were unblinded for safety or ethical reasons, were excluded.

The FDA NDA application and EMEA EPAR were available from the internet and provided detailed information on the trials considered in the licensing application for anakinra in the US and Europe respectively. Clinical trial reports on four trials were provided in Amgen's submission to NICE. These were considered in conjunction with the RCT reports.

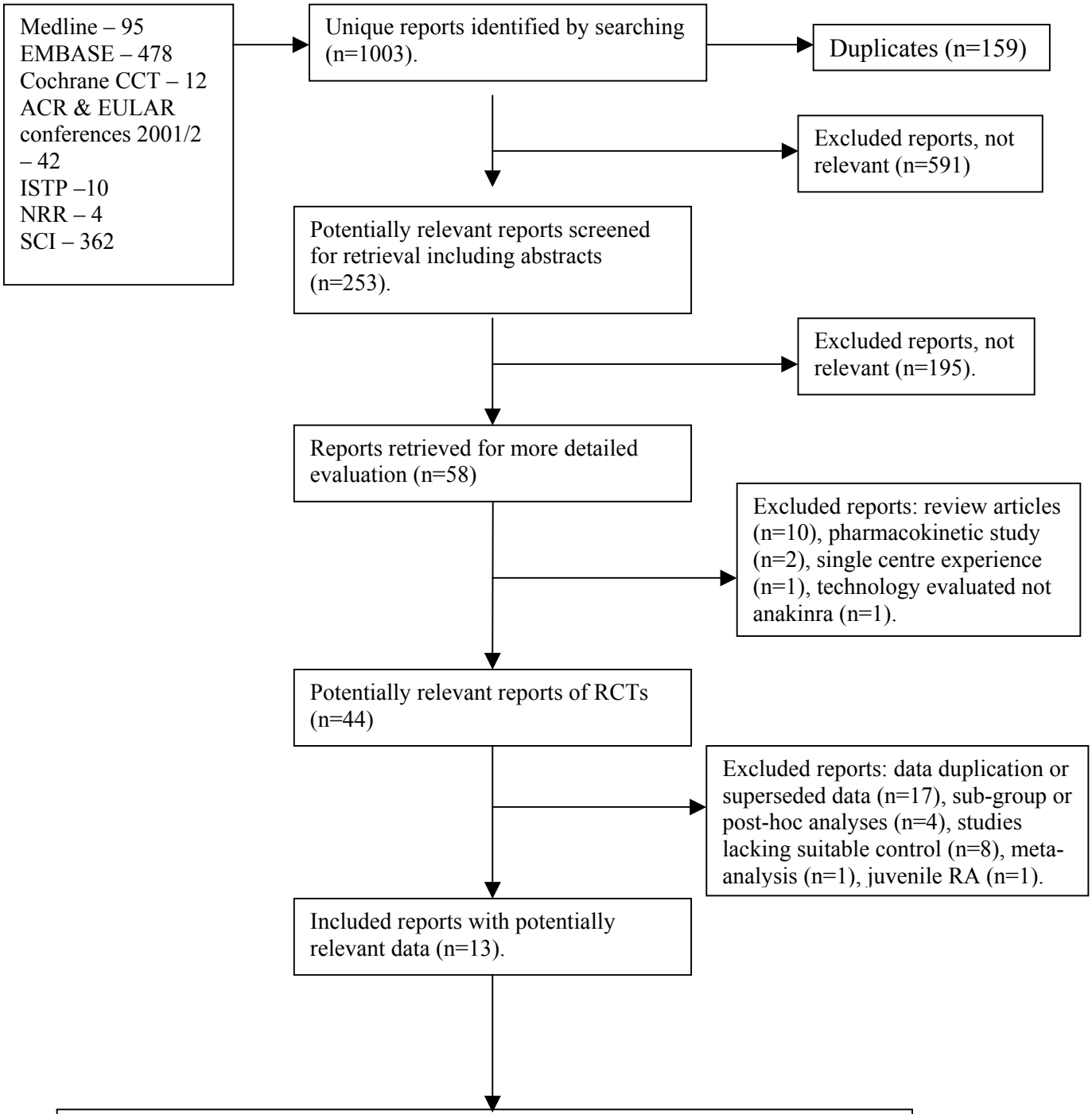
Five RCTs of anakinra were included in the review, two as monotherapy, and three in combination with DMARDs, one of which was principally a safety study. Only one efficacy trial and the safety study specifically evaluated anakinra at a dose of 100mg/day (licensed dose).

CONFIDENTIAL INFORMATION REMOVED.

A flow diagram illustrating the volume of literature identified and the selection of relevant reports is shown in Figure 1. A list of included and excluded reports, with a brief comment and reasons for exclusion, is shown in Appendix 6, page 94. Additional trials of anakinra in RA are currently in progress.

In evaluating adverse events with anakinra data from the included studies, post-marketing surveillance and other experiences are evaluated and discussed.

Figure 1 Flow diagram for identified reports.



3.2.3 Quality and Efficacy

Five trials, which met the inclusion criteria, were identified; four efficacy trials (two monotherapy [0560,[102] 0182 [103]], two in combination with MTX [0180,[104] 0145[105] [103]]) and one safety study (combined therapy [0757][106,103]. Four were identified from electronic searches and one from the FDA and EMEA licensing submissions. A description of the included studies is given in Table 4, page 47.

The four efficacy trials have all been completed but fully published data are only available for two. The low dose ranging trial (2.5 - 30mg/day), 0182, has never been published and the largest efficacy trial, 0145 has just been completed. Currently only interim and preliminary endpoint data are available. The safety study (0757) is still ongoing, interim data are currently available. The large efficacy trial (0145) and the safety study (0757) both evaluated anakinra at a dose of 100mg/day, the other studies considered ranges of doses.

All included trials were of high quality.

Table 3: Summary of JADAD scores for included studies

Study	Truly random allocation	Was concealment adequate?	Was treatment allocation masked from:			Significant difference in completion rates between groups	JADAD score
			Participants	Investigators	Assessors		
560[102;107]	Yes	Yes	Yes	Yes	Yes	No	5
0182[103] 108	Yes	Yes	Yes	Yes	Yes	No	5
0180 [104] 103;109	Yes	Yes	Yes	Yes	Yes	No	5
0145 105;110	Yes	Yes	Yes	Yes	Yes	No	5
0757[106] 103;111	Yes	Yes	Yes	Yes	Yes	No	5

All trials were described as double-blind with active and control medication having similar appearance. There is however the potential that unblinding occurred due to differences in adverse event profiles of the treatments, particularly injection site reactions. This is discussed in more detail later in the report.

A description of the study characteristics and key data are given below for each trial. Results from all trials are tabulated.

3.2.3.1 Anakinra monotherapy

Two short-term dose ranging placebo controlled trials have evaluated the efficacy of anakinra monotherapy in the treatment of RA. The study by Bresnihan and colleagues is published in

full. [102] Data on the smaller dose ranging study are only available in the FDA NDA submission and European centralised marketing authorisation application. [101;103]

Study 0560 - Bresnihan and colleagues 1998[102;103;107]

Population:
This phase II dose ranging study enrolled adult patients with active RA as defined by ACR criteria. Patients did not have to have failed, or been intolerant of, prior DMARD treatment. For those who were on DMARD treatment prior to enrolment, this treatment had to be withdrawn at least 6 weeks before entry.

A total of 473 patients from 41 centres across 11 European countries were enrolled. Patients were aged between 18-75 years (mean 53.1 years) were almost exclusively white (99%) and predominantly women (75%). Patients had active disease with a median of 32 to 35 tender and 25 to 26 swollen joints, median HAQ of 1.5 or 1.6, median CRP of 2.7 to 3.2 mg/dl and a mean ESR above 45mm/hr at baseline. Median disease duration was 3.3 years for placebo and 3.9 years for anakinra. Patients had received a median of 1 previous DMARD, and 36% had previously received methotrexate. Nearly a quarter of all patients had not received any previous DMARD (116 of the 473 patients; 19-34% across the treatment groups). Patients were permitted to continue treatment with NSAIDs and low dose oral corticosteroids (taken by 83.5 % and 42.6% respectively) provided that drug doses remained constant during the trial. Approximately 70% of patients were rheumatoid factor positive and 73% had erosions on baseline radiographs.

At baseline notable differences across the treatment groups were fewer men, lower previous DMARD use and fewer erosions in the highest anakinra dose group.

Interventions:
All interventions were given as a single daily subcutaneous injection administered by the patient or caregiver. Patients were randomised to one of 4 treatment groups:

- Placebo n= 121
- Anakinra 30mg/day n=119
- Anakinra 75mg/day n=116
- Anakinra 150mg/day n=116

One patient withdrew before receiving study medication.

Study duration and key outcomes:
24 weeks – the primary outcome measure was ACR composite score & Paulus criteria. Nine secondary efficacy outcome measures were pre-specified. The Larsens score and erosive joint count were also evaluated.

Main efficacy results:
With modified intention to treat analysis 27%, 39%, 34% and 43% patients met the ACR20 response criteria at week 24 when treated with placebo and anakinra 30mg, 75mg, 150mg respectively (p=0.047, 0.276, 0.014 for each dose versus placebo). Similar responses were documented using Paulus criteria with 20% response in 21%, 39%, 37% and 44% patients respectively.

Sustained ACR20 response, defined as ACR20 response for 4 of the 6 study months, one of which must be observed at week 12 or 24, was achieved by 11% patients treated with

placebo, 28%, 28% and 24% of patients treated with anakinra 30mg, 75mg and 150mg respectively (p= 0.0009, 0.0005, 0.0083 vs placebo). ACR50 responses occurred in 8% of placebo patients, 13%, 10% and 18% with increasing doses of anakinra (LOCF method). ACR70 responses occurred in less than 1% of cases except for the group treated with anakinra 30 mg (4%).

The mean change from baseline in the components of the ACR were all significantly reduced with the highest dose of anakinra. Consistent changes across all these criteria were not evident for the other two doses of anakinra evaluated. Refer to Table 6, page 50.

The duration of EMS was only significantly reduced with 75mg anakinra vs placebo (p=0.006). Hand radiographs were available for 74% of the patients at baseline and 24 weeks. The mean Larsen score increased by 6.4 (from a baseline of 15.4) with placebo compared with increases of 3.8, 3.9 and 4.0 respectively with increasing doses of anakinra (p=0.04, p=0.09 and p=0.11 comparing anakinra with placebo). The number of joints with erosions increased by 2.6 with placebo (5.0 at baseline) compared with increases of 1.5, 1.0 and 1.7 respectively with increasing doses of anakinra (p=0.02, p=0.004 and p=0.074 comparing anakinra with placebo).

Twenty seven % of patients dropped out of this trial prior to the 6 month primary endpoint with the highest drop out occurring in the placebo group (26% placebo vs 20%, 19% & 24% anakinra 30mg, 75mg & 150mg respectively). Of the completers 37% of placebo patients achieved ACR20 response at 24 weeks compared with 49.5%, 42% and 52% with increasing doses of anakinra (p = 0.12, 0.56 and 0.04 respectively). One patient allocated to anakinra withdrew before receiving study medication. Of the remaining withdrawals 20% patients on placebo and 12% on anakinra (all doses) withdrew due to lack of efficacy and 4% vs 9% respectively for adverse effects.

Adverse events:
These were reported in detail in an internal company report. Severe adverse events, as defined by the FDA, occurred in 12% of placebo treated patients compared with 8%, 15% and 16% with increasing doses of anakinra.

The most frequent adverse event was injection site reactions (ISRs: 25% placebo, 50%, 73%, 81% respectively with increasing anakinra). Most ISRs were graded ‘mild’ or ‘moderate’ but some took 2-3 weeks to resolve. Symptoms of ISRs included local irritation, pain or urticaria. Patients experiencing ISRs usually reported them within 28 days of starting treatment. No ISR was recorded as a serious adverse event but ISRs led to study withdrawal in 2% of placebo treated patients, and 1%, 3% and 5% of anakinra patients with increasing dose of anakinra. Worsening of joint pain was reported by 50% of placebo treated patients and, 48%, 42%, and 38% respectively for anakinra 30mg, 75mg and 150mg doses. Headaches were reported in 6% patients on anakinra 150mg compared to 1% with placebo (no further details given).

Infections occurred in 38% patients treated with placebo and 37% treated with anakinra (all doses). The most common infections were upper respiratory tract infections (URTI), influenza like symptoms and urinary tract infections (UTIs). Infections resulting in antibiotic therapy occurred in 12% placebo treated and 15-17% anakinra treated patients. Six patients were hospitalised for infections, 4 in the 150mg anakinra group. Serious infections were

reported in 7 patients ; placebo (1 URTI), 75mg (2; URTI and bursitis), 150mg (4; UTI/URTI, Herpes Zoster and 2 bursitis) anakinra.

Three patients given anakinra were withdrawn due to neutropenia (<2.0 x 10^3/μl; as required by study protocol). Clinical symptoms were not seen and neutrophils recovered on drug withdrawal. In three patients, one in each anakinra arm, anti-IL1-Ra antibodies were detected at two or more follow up visit (titres of between 1:50 to 1:800).

Four patients on anakinra [30mg (2), 150mg (2), none receiving placebo or 75 mg] developed a malignancy during treatment (lung cancer, oral squamous cell cancer, basal cell carcinoma, thyroid cancer). A further patient who received 30mg anakinra was diagnosed with small cell lung cancer 3 weeks after completing the study. These were all considered unrelated to the study drug.

Comments
Patients were enrolled if they had had RA for > 6 months but less than 8 years. Thus patients were at an early stage of disease and 59% of patients had received fewer than 2 DMARDs at inclusion. Patients who had failed to respond to 3 or more previous DMARDs were excluded however 4 patients were reported as having received 4 previous DMARDs at baseline. Differences between groups at baseline in terms of DMARD use did not predict response to anakinra.

It seems likely that unmasking to treatment allocation occurred during the study due to the high rate of ISRs in patients receiving anakinra, particularly the 150mg dose.

The modified intention to treat analysis included all patients who had taken at least one dose of study drug and had at least one post-baseline evaluation. No adjustment for multiple comparisons was undertaken in the reporting of the trial results. P values quoted in the papers are thus nominal values. If a Bonferroni adjustment for multiple comparisons were applied p values would have to be less than 0.017 for significance at the 0.05 level to be retained.

Sensitivity analyses were reported, in an internal company report, by assuming that subjects with missing data or unusable data at week 24 had not responded. Reported p values comparing anakinra with placebo were 0.033, 0.186 and 0.033 for anakinra 30, 75 and 150 mg respectively.

The trial protocol specified that radiological progression of the disease would be assessed by the Larsens score and erosive joint count (EJC) following defined methodology. A post-hoc analysis re-reading the data using different methodology was undertaken to calculate a modified Sharp score. The results from this re-analysis suggested that anakinra may have activity in inhibiting radiological progression. However data from 133 patients was not included in this re-analysis. Caution is therefore advised in the interpretation of this post-hoc analysis. The FDA state ‘ the lack of statistical significance of the primary analysis and large amount of missing data (26%) limit the conclusions that can be based on this data.’ The re-analysis using Sharp score is not therefore considered in this evaluation.

Study 0182 – unpublished [101;103;108]
This European randomised controlled trial was a phase 1 pilot study, conducted in 15 centres across 6 European countries in 1997. It was undertaken to evaluate the efficacy of lower doses of anakinra.

Population:
Adult patients (≥ 18 years of age) with active RA for at least 6 months but less than 8 years were enrolled into this trial. Patients had to have ≥ 10 swollen joints and were not permitted to use DMARDs during the study. DMARDs were discontinued at least 6 weeks before study entry with the exception of ciclosporin, which had to be stopped 6 months before the trial commenced. Treatment with NSAIDs and/or low doses of oral corticosteroids could be continued provided doses were stable for at least 4 weeks before entry.

A total of 141 patients were randomised to treatment for 12 weeks. Of 141 patients 108 (77%) were female. Patients had a mean age of 52 years (range 25-80) and all were white. The majority (79% to 93%) of patients were using NSAIDs at baseline and 38% to 50% were receiving corticosteroids. Patients had active disease with an average of 32 to 36 tender/painful joints and 23 to 25 swollen joints, mean HAQ of 1.5 to 1.7, and mean ESR of 40 to 47 mm/hr. Mean CRP concentrations were higher in the placebo group (4.2mg/dl) than in the anakinra groups (2.7 to 3.1 mg/dl). Mean disease duration was also higher in the placebo group (4.9 years) than in the anakinra treatment groups (2.7 to 3.7 years) as was the median number of previous DMARDs (2.0 vs 1.0). Of placebo treated patients, 53% had previously used methotrexate compared with 29-40% anakinra treated patients. At baseline 59% to 76% patients across the treatment groups were positive for RF.

At baseline notable differences in baseline characteristics were longer mean duration of RA, higher proportion of methotrexate use, lower proportion of DMARD-naïve subjects, higher mean CRP concentration, higher RF titres in the placebo group.

Interventions:
All treatments were given by subcutaneous injection, once daily. Patients were randomised to:

- Placebo n= 30
- Anakinra 2.5mg/day n=42
- Anakinra 10mg/day n= 40
- Anakinra 30mg/day n=29

Study duration and key outcomes:
12 weeks – Primary endpoint ACR 20 response at week 12

Secondary endpoints included change from baseline in ACR components at week 12, ACR50 ACR70, duration of morning stiffness and ESR.

Main efficacy results:
No statistically significant effects of anakinra on primary or secondary endpoints were documented.

ACR 20 response was seen in 43% placebo treated and 26%, 28% and 34% patients treated with anakinra 2.5mg, 10mg, and 30mg respectively.

Twelve % of patients withdrew prematurely; 10% placebo, 19%, 7.5%, 10% anakinra 2.5mg, 10mg and 30mg respectively.

Adverse events:
Anakinra was well tolerated with 5.4% patients withdrawing from treatment due to an adverse reaction. Adverse events occurred at comparable rates across the treatment groups (including infections). The most frequent event was RA flare; 17% on placebo and 14% on anakinra. ISRs were reported in 3% placebo and 12%, 18% and 35% of patients treated with anakinra 2.5mg, 10mg, 30mg/day.

No changes in WBC counts were documented. Antibodies to anakinra were seen in 5% of anakinra treated patients.

Comments:
Intention-to-treat (ITT) analysis was undertaken for all randomised patients who received at least one dose of study drug with non-responder imputation.

Despite the placebo response rate in this trial being higher than that seen in the other efficacy trials with anakinra, the ACR response seen with the low doses of anakinra was low and cannot be considered different to that achieved with placebo.

3.2.3.2 Anakinra in combination with DMARDs/ MTX

Two trials have evaluated use in combination with MTX, only one of these is completed and published in full.[104] The second trial is a one year study which focuses on the effect of treatment on disease progression. Whilst this trial is now completed, full data on the one year endpoint are not yet available. Data to 6 months (for a sub-set of patients) on the effect of treatment on ACR responses is reported in an abstract[105], the FDA and EMEA submission documents and the clinical study report provided by Amgen in confidence. A third trial, a pragmatic safety study, evaluated use in combination with DMARDs.[106]

Study 0180 – Cohen and colleagues 2002[104;109]

Population:
Patients enrolled in this trial had active RA despite treatment with methotrexate for at least 6 months (15-25mg/week). The dose of methotrexate had to have remained stable for at least 3 months before study entry and was maintained at this level throughout the trial. Patients received folic acid to reduce methotrexate toxicity.

Concomitant treatment with other DMARDs was not permitted. These were discontinued at least 12 weeks before study entry with the exception of hydroxychloroquine and sulfasalazine which were discontinued at least 8 weeks before entry. Treatment with NSAIDs and low dose oral corticosteroids (≤ 10mg/day of prednisolone or equivalent) was permitted provided doses were stabilised for 4 weeks before study entry and for the duration of the trial.

Active disease was defined as at least 6 swollen joints and the presence of at least two of the following:

- At least 9 tender and painful joints

- Morning stiffness lasting at least 45 minutes
- CRP of greater than 1.5mg/dl

A total of 419 patients participated in this study across 36 centres in the US, Canada and Australia. The design was however complicated by a change to the original trial protocol (see comments below). 419 patients were evaluated at the 12 week endpoint of whom 317 were also evaluated at the 24 week endpoint.

The mean age of patients enrolled in the trial was 52.5 years and mean disease duration 7.5 years. Over 80% of patients were white and 66.5% female. Excluding methotrexate the median number of previous DMARDs was 2.0 for all groups except for patients treated with 0.4 and 2.0 mg/kg/day who had received a median of 1.0 previous DMARD. Twenty % of placebo patients and 14%, 19%, 31%, 27%, and 23% of anakinra patients (in increasing doses) had not received any other DMARD previously. NSAID use (68.9%) and oral corticosteroid use (64.1%) varied across the groups but was generally comparable between control and the higher anakinra doses evaluated (1.0 & 2.0mg/kg/day). 70-80% patients were rheumatoid factor positive at baseline.

The median dose of methotrexate at baseline was 15 mg/week for all groups except patients on 0.04 and 0.1 mg/kg/day of anakinra who received 17.5 mg and 15.6 mg per week respectively. Patients had a mean of 18 swollen and 25 tender joints at baseline. The mean tender joint count varied across the treatment groups with the highest level seen in the control group (28) and the lowest in patients treated with anakinra 1.0mg/kg/day (22 joints). Mean baseline ESR ranged from 35.1 to 37.9 mm/hr across treatment groups. Refer to Table 5: Disease activity at baseline across the treatment groups (mean (SEM) or ± SD), page 49. Median HAQ scores for all groups were either 1.4 or 1.5 at baseline.

Intervention:
Study drugs were all administered by subcutaneous injection once daily by the patient or caregiver. Rotation of the injection site was advised. Patients were randomised to:

- Control (MTX alone) n=74 12 weeks, n= 48 24 weeks
- Anakinra 0.04mg/kg/day n= 63, 12 & 24 weeks
- Anakinra 0.1mg/kg/day n= 74 12 weeks, n= 46 ,24 weeks
- Anakinra 0.4mg/kg/day n= 77 12 weeks, n= 55 24 weeks
- Anakinra 1.0mg/kg/day n= 59 12 & 24 weeks
- Anakinra 2.0mg/kg/day n= 72 12 weeks, n= 46 24 weeks

Study duration and key outcomes:
12 weeks subsequently amended to 24 weeks – primary efficacy endpoint was ACR 20 at week 12.

In addition to ACR 20 response at week 24, 11 secondary efficacy endpoints were specified including ACR50 and ACR70. All but one (sustained ACR 20 response) were assessed at both 12 and 24 weeks. A sustained ACR20 response was defined as an ACR20 response for at least 4 out of the 6 months of therapy (not necessarily consecutive), one of which was at weeks 12 or 24.

Main Results:

ACR 20 response at 12 weeks was 19% with control and 25%, 35%, 25%, 46% and 38% with anakinra 0.04-2.0mg/kg/day respectively. A significant dose response was seen (p=0.001) across the anakinra groups. The proportions of patients showing ACR20 responses were significantly greater for 0.1, 1.0 & 2.0mg/kg/day of anakinra compared with control (p=0.014, 0.001 & 0.007 respectively). Similar results were apparent for ACR20 at 24 weeks but a significantly improved response was only apparent with the 1.0mg/kg/day dosage group (p=0.018 vs control). ACR20 responses were evident from week 2 but statistically significant differences between active and control treatment did not appear before week 4.

A sustained ACR20 response (see above for definition) was seen more frequently for anakinra 0.1,1.0 & 2.0mg/kg/day compared to control (30%, 31%, 35% respectively vs 15% with control; $p<0.05$ for all).

The proportion of patients achieving ACR50 and ACR70 was higher at all doses of anakinra evaluated (with a significant dose response) compared to control at both time points. ACR50 responses at week 24 were 4% for control and 8%, 13%, 9%, 14% and 11% for anakinra groups with increasing dose. ACR70 responses at 24 weeks were 0% for control and 5%, 6.5%, 2%, 10% and 6.5% for anakinra groups with increasing dose. Statistical tests to assess the significance of these improvements compared to control are not reported but only 16 patients of 345 treated with anakinra showed ACR70 responses at weeks 12 or 24.

The 'adjusted' mean change from baseline in the components of the ACR criteria are presented for control versus anakinra (refer to Table 6, page 50). At week 24 statistically significant changes from baseline compared to control were apparent for swollen joint count (2.0mg/kg/day only), pain (0.1, 1.0 & 2.0mg/kg/day only), physicians global assessment (1.0mg/kg/day & 2.0mg/kg/day), patients global assessment (0.1, 1.0 & 2.0mg/kg/day), HAQ (1.0 & 2.0mg/kg/day) and ESR (0.4, 1.0 & 2,0mg/kg/day). The improvements in tender joint count, CRP and duration of morning stiffness did not reach statistical significance.

Eighty eight patients (21%) withdrew from the study; 19% control and 21%, 16%, 22%, 22% & 26% across the anakinra dose groups. Withdrawals were due to lack of efficacy in 7%, 14%, 10%, 8%, 7% & 6% of patients respectively.

Adverse events:
Across the dosage groups 4% patients on control, 3%, 1%, 7%, 14% and 15% patients on anakinra 0.04-2.0mg/kg/day withdrew from the study as a result of adverse events. ISRs were the most common adverse reaction encountered and increased in frequency with increasing anakinra dose; 28% control, 19%, 38%, 56%, 64%, 63% anakinra 0.04-2.0mg/kg/dose. These were generally mild to moderate and diminished with time. ISRs led to withdrawal from treatment in 3%, 0%, 0%, 1%, 7% and 10% respectively across the groups.

The second most frequently reported side effect, potentially related to anakinra, was headache seen in 15% placebo, 24%, 20%, 17%, 34% and 14% patients in the 0.04-, 0.1-, 0.4-, 1.0-, and 2.0-mg/kg/day anakinra groups respectively.

Severe adverse events were reported in 19% patients treated with placebo compared with 8-18% treated with any dose of anakinra studied. No deaths were reported during the study. Two patients (1 control, 1 anakinra 2.0mg/kg/day) were diagnosed with a new malignancy during the study (lung cancer, breast cancer) neither was considered related to the study drug.

Other adverse drug reactions (ADRs) were not reported in detail. URTI was documented in 22% patients treated with control compared with 14-24% treated with anakinra, sinusitis (15% vs 5-14%) abdominal pain (1% vs 6%), arthralgia (7% vs 6%) and worsening of RA (11% vs 6%). Serious infections occurred in 7 patients in total; 1 control, 2 anakinra 0.04mg/kg/day, 1 anakinra 0.1mg/kg/day, 1 anakinra 0.4mg/kg/day and 2 anakinra 1.0mg/kg/day.

Five cases of neutropenia (one in each anakinra dose group) occurred during the course of the study. In all cases patients were withdrawn from treatment and white blood cell (WBC) levels returned to normal.

Antibodies to IL-1Ra were detected in 9 of the 354 patients screened; 1 control, 8 anakinra. Seven of the 8 patients who developed these antibodies suffered with injection site reactions.

Comments
This trial represents the first study to explore anakinra in combination with methotrexate.

The design of this study was complicated by a change to the initial protocol. The study was originally designed to evaluate the 12 week efficacy of anakinra across 3 doses (0.1,0.4, 2.0mg/kg/day). It was subsequently amended to a 24 week study and included two additional doses of anakinra (0.04 & 1.0mg/kg/day). Of the 105 patients originally enrolled in the 12 week trial only 3 re-consented and remained in the trial to 24 weeks. The impact of this self selection is unlikely to significantly undermine the results of this study due to the small numbers of patients involved.

Results were analysed by intention to treat with non-responder imputation. Adjusted mean changes were reported adjusted for study centre and baseline value.

Again there is the potential for unblinding due to the high frequency of injection site reactions with anakinra.

Study 0145 – Cohen and colleagues 2001 [103;105;112]

Population:
Patients enrolled in this trial had active RA despite treatment with methotrexate for at least 24 weeks (10-25mg/week) at a stable dose for at least 8 weeks before study entry. Patients also took folic acid at a dose of approximately 1mg/day. At baseline evidence of at least one bony erosion was required.

Active disease was defined as at least 6 swollen and 9 tender joints and a CRP level ≥ 1.5 mg/dl or ESR ≥ 28mm/hr.

Concomitant treatment with DMARDs other than MTX had to be discontinued at least 60 days before study entry. Treatment with NSAIDs and low dose oral corticosteroids (≤ 10mg/day of prednisolone or equivalent) was permitted provided patients were on a stable dose for at least 4 weeks before study entry. Rescue analgesics were allowed up to 12 hours before a scheduled study evaluation and intra-articular corticosteroids could be administered to 2 joints on two separate occasions (doses not specified) provided that injections were at

least 2 weeks prior to the next assessment visit. The treated joint was thereafter classified as a 'failed' joint in the joint assessment. The protocol permitted use of NSAIDs or oral steroids (or increases in dose), temporarily, for flare of RA symptoms. However written permission was required for changes in steroid doses.

A total of 906 patients were recruited into this trial across 106 centres in the US, Canada and Australia. 506 were included in the interim analysis.

The mean age of patients enrolled in the trial was 56.3 years, mean disease duration 10.8 years. 87% of patients were white and 77% female. Patients had a mean of 20 swollen and 26 tender joints at baseline. The number of previous DMARDs used was not stated. NSAID use (76.4%) and oral corticosteroid use (52.7%) were comparable in both groups. 76.8% patients were rheumatoid factor positive at baseline. The median dose of methotrexate at baseline was 15mg/week and median HAQ scores 1.38 in both groups. Mean baseline ESR was 42 mm/hr and CRP 2.6 mg/dl.

Intervention:
Study drugs were all administered by subcutaneous injection once daily by the patient. Patients were randomised to:

- Control (MTX alone) n=253 24 weeks (453 for 52 weeks)
- Anakinra 100mg n= 253 24 weeks (453 for 52 weeks)

Study duration and key outcomes:
The primary endpoint was radiographic progression measured by modified Sharp score at 1 year. However a 6 month interim analysis was undertaken on the 506 patients enrolled in the trial as of 18th May 2000 with ACR20 as a primary endpoint. Sustained ACR20 response, ACR50, ACR70 and other components of disease were secondary endpoints. Sustained ACR20 response was defined as an ACR20 response for at least 4 out of the 6 months of therapy (not necessarily consecutive), and one of which was at weeks 12 or 24.

The study blind, for the primary outcome of radiographic progression, was maintained during the interim analysis.

Main Results:
ACR 20 response at 24 weeks was 22% with MTX and placebo (control) vs 38% for anakinra 100mg + MTX, $p<0.001$. It was assumed that where ACR responses could not be calculated because of missing data ACR response did not occur ('non-responder imputation'). Similarly patients who increased their baseline dose of methotrexate or corticosteroids were classified as non-responders from the time of dose increase. A significant difference in ACR20 response between the groups was apparent from week 4. The ACR response increased to week 12 in patients on control and then plateaued. For patients on anakinra + MTX ACR 20 response continued to increase to at least week 20.

Sustained ACR20 response was reported in 12% patients treated with control and 27% treated with anakinra +MTX, $p<0.001$.

The proportion of patients who achieved ACR50 and ACR70 was 17% and 5.6%, respectively, with anakinra + MTX compared with 8% and 2% with control ($p=0.001$ and $p=0.024$).

The mean reduction in swollen joints for patients treated with control was 6.5 joints (total assessed 66) compared with 6.8 for anakinra + MTX (p=0.686) at 24 weeks. This result is surprising since an ACR20 response requires a 20% improvement in swollen *and* tender joints as well as three other disease components (from physician and patient global, patient's assessment of pain, disability score and ESR or CRP). These other disease parameters showed significant differences when comparing anakinra + MTX and control (Refer to Table 6, page 50).

Over 6 months, 67 (26.5%) patients on control and 56 (22.1%) on anakinra withdrew from the study. Two patients randomised to control and 3 to anakinra did not receive study drug and were excluded from the ITT analysis. Of the other withdrawals 29 (12%) patients on control and 12 (5%) on anakinra withdrew at the subjects request and 10 (4%) vs 3 (1%) because of disease progression. Lack of efficacy per se was not specified as a reason.

Adverse events:
Withdrawals due to adverse events are reported to have occurred in 9% of patients on control and 13% on anakinra. Injection site reactions were the most common adverse event and occurred in 24% control and 65% anakinra treated patients, leading to withdrawal from the study in 0.8% and 8.4% respectively. These reactions were generally mild to moderate and transient.

Infectious episodes occurred in 26% of control treated patients compared with 33% for anakinra, but there were similar numbers of serious infections (0.8%). Serious adverse events, affecting a variety of body systems, occurred in 8 (3.2%) of control patients and 11 (4.4%) anakinra patients. No patients died whilst receiving study drug, though one patient died of congestive heart failure 37 days after discontinuing study drug (anakinra).

Comments:
This trial was complicated by allowing a 'Lack of Efficacy' (LOE) designation after 16 weeks. LOE designation was defined as a failure to achieve ACR 20 response on 3 consecutive visits spanning 8 weeks. These patients continued with study drug and had their regimen optimised by changing their methotrexate, corticosteroid and/or NSAID doses. If patients continued to meet the LOE criteria after these dosage changes then hydroxychloroquine, sulfasalazine, gold, minocycline, leflunomide or ciclosporin could be added. Nineteen patients (7.6%) in each arm increased corticosteroid or DMARD usage (8 patients on control because of failure to meet efficacy criteria and five patients on anakinra). Subjects who required a change in their base-line medication due to LOE were classified as non-responders for the ACR20.

In order to prevent assessors becoming aware of treatment allocation due to ISRs independent assessors were used to evaluate swollen and tender joint counts.

Results, for the interim analysis, were analysed by intention to treat for all randomised subjects who received at least one dose of study drug (n=251 control, n=250 anakinra + MTX), with non-responder imputation. Sensitivity analysis around the primary endpoint conducted by the FDA identified that the difference in ACR20 response rates between control and anakinra remained statistically significant when the analysis was adjusted to:

- a completer analysis

- consider only patients with no injection site reaction
- count patients who responded after a change to their treatment regimen as responders not failures.

Subset analysis by the FDA found no evidence that the benefit from anakinra was limited to any identifiable subset of RA patients in terms of age, sex, ethnicity, disease duration, RF status & acute phase reactants at baseline, and baseline level of disease activity.

This one-year trial, with a planned recruitment of 990 patients, was designed to evaluate radiographic outcome using the modified Sharp total score at 12 months. Only limited data are currently available. Preliminary analysis suggests that anakinra + MTX inhibits joint destruction compared to MTX alone (change from baseline to week 52 in total modified Sharp score; p=0.002). This effect on disease progression was also apparent in patients who failed to achieve an ACR20 response at week 24.

Study 0757 – Fleischman and colleagues 2001[106]
This large randomised placebo controlled international study was undertaken to evaluate the safety of anakinra in the "usual RA patient seen in clinical practice".

Population
Adult patients (age ≥18 years) with RA for at least 3 months were enrolled. Those on DMARDs either as monotherapy or combination therapy had to be on stable doses for at least 2 months. Concomitant treatment with NSAIDs and/ or low dose oral corticosteroids (doses stabilised for at least 1 month) was also permitted. A minimum of 3 swollen and 3 tender/painful joints or morning stiffness of at least 45 minutes were required for entry.

Changes in NSAIDs, corticosteroids or DMARDs were permitted during the study as clinically needed. The following drugs however were not permitted; etanercept, infliximab, mycophenolate mofetil, cyclophosphamide, ciclosporin and prosorba column.

A total of 1414 patients in Australia, Belgium, Canada, Germany, Ireland, Sweden, UK and the US were enrolled. Over 80% patients were enrolled in the US. The trial was double blinded and controlled for the first 6 months with an open label extension to 3 years (still ongoing).

The mean age of patients enrolled in this trial was 55 with 23.0% patients aged 65 or over. Mean disease duration was 10.2 years (median 7.5 years), 88% patients were white and 75% were female. Patients had a mean of 19 swollen and 23 tender joints at baseline. Mean baseline CRP was 2.7 mg/dl (median 1.7).

DMARDs were taken by 82% of patients on control and 78% of patients randomised to anakinra. Figures for MTX were 59% and 52% respectively with a mean (and median) dose of MTX of 15mg/wk in both groups. After MTX the most common DMARDs were hydroxychloroquine (22% patients) sulfasalazine (14%) and leflunomide (10%). Combinations of DMARDs were being given to 30% on control and 28% on anakinra.

At baseline a high proportion of patients were on NSAIDs (87%) and corticosteroids (58%) with similar usage in both groups.

Intervention:
Study drugs were administered by subcutaneous injection once daily. Patients were randomised to treatment in a 1:4 ratio.

- Control (placebo + current DMARD regimen) n= 284
- Anakinra 100mg/day n= 1130

Study duration and key outcomes
3 years – the primary endpoint for this ongoing study is safety, evaluated by death, serious and severe adverse events and discontinuation from the study due to adverse events.

This study was controlled and blinded to 6 months with open label anakinra planned for 3 years. Safety data for the 6 month controlled trial are available. The open-label phase will complete at the end of 2002. No efficacy endpoints have been reported and none are currently available from Amgen.

Results were analysed by intention to treat for all randomised subjects who received at least one dose of study drug (n= 283 control, n=1116 anakinra).

Main results

By 6 months 54 of 284 (19%) of the patients allocated control and 255 of the 1130 (23%) patients allocated anakinra had withdrawn prematurely. Withdrawal because of an adverse event occurred in 6% and 11.5% respectively. Consent was withdrawn by approximately 6% of patients in each group before completing 6 months.

ISRs in particular were more common with anakinra and occurred in 73% vs 33% control patients. ISRs led to withdrawal in 7% vs 1% patients respectively. Anakinra caused ISRs that were described as erythema, pruritus or rash whereas control caused ISRs reported as pain or ecchymoses. Most ISRs occurred within one month but the duration of each ISR was not determined.

Respiratory events were experienced by 34.6% control treated and 35.0% anakinra treated patients, and consisted primarily of URTI and sinusitis. Pneumonia or bronchopneumonia occurred in 2 control (0.7%) patients and 15 (1.4%) anakinra patients, leading to withdrawal in 5 of these 15. Musculoskeletal pain and worsening of RA occurred more commonly in control treated patients and led to withdrawal in 3.5% of patients compared with 2.1% for anakinra treated patients.

Five patients died during the 6 month study; 1 on control (0.4%) and 4 on anakinra (0.4%). Causes of death were MI (control), pulmonary fibrosis, suicide, melanoma and upper gastrointestinal bleed (anakinra).

Serious adverse events were reported in 7.8% control treated and 7.7% anakinra treated patients. By body system a higher proportion of serious adverse events was seen with anakinra for the gastrointestinal (2% vs 0.4%) and respiratory (2% vs 0.4%) systems. Severe adverse events were reported in 13.1% control and 15.5% anakinra treated patients.

The overall incidence of infections was similar for control and anakinra: 43.5% vs 41.2%. However severe infections were more common with anakinra: 2.1% vs 0.4% . None were

fatal. The most common severe infections seen with anakinra were pneumonia (10 patients), cellulitis (3 patients) and osteomyelitis (3 patients). Patients who developed infections tended to be male and older.

A total of 9 malignancies were reported during the 6 month study; 4 (0.4%) anakinra vs 5 (2%) control.

Comments
This large pragmatic trial was concerned with safety but it also provides effectiveness data for anakinra, in a typical clinical population of patients with RA. The first six months of the trial when efficacy data were collected, was blinded. ACR assessments were undertaken at screening and at month six. All data collection for the 6-month endpoints was completed by 26th July 2000. The effectiveness data from this trial was requested from Amgen. The pharmaceutical company declined to make it available. They issued the following statement:

> *"Study 990757 was designed to evaluate the overall safety of anakinra in 1,414 patients with rheumatoid arthritis (RA) in the average clinical practice to contrast against the more controlled patient populations enrolled in previous studies. The primary safety endpoints assessed the incidence of: adverse events, deaths, serious adverse events, and adverse events leading to withdrawal, and infections. No efficacy endpoints were planned for the study. This study included patients receiving a variety of concurrent RA medications including multiple DMARD therapies, as well as patients who were DMARD-free. Concurrent DMARDs included MTX, sulfasalazine, hydroxychloroquine, gold, penicillamine, leflunomide, and azathioprine. The study population also included patients predisposed to infection due to a history of underlying disease such as pneumonia, asthma, controlled diabetes, and chronic obstructive pulmonary disease. Patients with co-morbidities such as hypertension, coronary artery disease and congestive heart failure were also included.*
>
> *Given the study was not designed to assess efficacy, and the varied patient population defined above, it would be inappropriate and misleading to draw any conclusions from any efficacy assessments taken from this study. Confounding factors such as disease duration, concomitant medications and co-morbid conditions make it difficult to define discreet patient populations in whom efficacy could be assessed and even where this is possible, the low numbers of patients in such analyses renders any clinical or statistical assessment invalid."*

It is not true that no efficacy endpoints were planned for the study. Table 7-1 of the study report shows that ACR scores (at the screening assessment and at six months) were collected prospectively. That this was planned from the start of the trial is confirmed in Table 7-2 of the study report, Summary of Protocol Amendments, which shows that making an ACR score assessment was not a later amendment.

Whilst the primary endpoint of this study was safety the non-disclosure of efficacy data is of concern, due to both the large size of this trial and its 'real life' design.

Concomitant diseases were present in 5-10% patients; COPD 5%, history of pneumonia (9%), asthma 9%, CAD 10%, DM 6%.

The study had 63% probability of observing ≥ 1 case of an adverse event occurring with an incidence of ≥ 0.1% over two and half years. At the 6 month endpoint there was a > 99% chance of detecting an adverse event occurring at a rate of 1%.

Table 4 : Description of Included Studies

Study & Description	Intervention & patient characteristics						
	Interventions *Anakinra and placebo were administered as once daily subcutaneous injections*	Patient nos.	Mean Age (years)	Disease duration (mean years)	No. of previous DMARDs (mean)	% On steroids	% on NSAIDs
Monotherapy- DMARDs not permitted							
Bresnihan, *et al.* 1998. [102;107] (0560) Study duration – 24 weeks. Placebo controlled RCT in 31 European centres of a range of doses of anakinra.	Placebo Anakinra 30mg/day Anakinra 75mg/day Anakinra 150mg/day	121 119 116 116	52 53 53 54	3.7 4.3 4.2 3.9	1.3 1.3 1.3 1.2	40.5 48.7 40.5 41.4	89.3 82.4 87.9 85.3
Study 960182[101;103 108] Study duration - 12 weeks Placebo controlled RCT conducted in multiple centres in Europe to evaluate the efficacy of lower doses of anakinra	Placebo Anakinra 2.5mg/day Anakinra 10mg/day Anakinra 30mg/day	30 42 40 29	51.7 54.2 52.3 49.8	4.9 2.8 3.7 2.7	2.1 1.4 1.6 1.4	50.0 38.1 47.5 41.4	93.3 78.6 90.0 82.8
Combination therapy with DMARDs							
Cohen, *et al*. 2002 [104;109] (0180) Study duration – 24 weeks Methotrexate controlled RCT in 36 centres across America, Canada & Australia to evaluate the efficacy of anakinra in combination with methotrexate	Placebo + MTX alone Anakinra 0.04mg/kg/day + MTX Anakinra 0.1mg/kg/day + MTX Anakinra 0.4mg/kg/day + MTX Anakinra 1.0mg/kg/day + MTX Anakinra 2.0mg/kg/day + MTX	(12 wk) 74 63 74 77 59 72	53.0 52.6 53.0 52.8 49.0 54.1	7.8 6.3 8.8 7.0 6.5 8.0	(Excl MTX) 2.1 2.0 1.9 1.4 1.8 1.9	66.2 68.5 64.9 58.4 62.7 65.3	67.6 79.4 70.3 67.5 64.4 65.3
Cohen, *et al*. 2001 [105;110] (0145) Study duration – 12 months (interim data to 6 months) Methotrexate controlled RCT in 106 centres across America, Canada & Australia to evaluate the effect of anakinra in combination with methotrexate on disease progression	Placebo+ MTX Anakinra 100mg/day + MTX	(interim analysis) 251[a] 250[a]	57.0 55.7	10.4 11.1	Not reported	52.2 53.2	77.3 75.6
Fleischman, *et al*. 2001[106;111] (0757) Study duration – 3 years (6 months double blind + remainder open label) International placebo controlled RCT in 169 centres to evaluate the safety of anakinra in clinical practice. Patients were permitted to continue with their current stable DMARD treatment	Placebo + current DMARD regimen Anakinra 100mg/day + current DMARD treatment	283[b] 1116[b]	56 55	11 10	Not specified	61 57	86 87

[a] 253 patients were randomised into each treatment arm, baseline characteristics are only provided for the 501 patients who were randomised and received at least one dose of study drug
[b] 284 patients were randomised to control and 1130 to anakinra treatment, baseline characterises are only provided for patients who received at least one dose of study drug

Table 5: Disease activity at baseline across the treatment groups (mean (SEM) or ± SD)

STUDY	SJC (0-66)	TJC (0-68)	Pain score patient	Global score		CRP (mg/dl)	ESR (mm/hr)	HAQ (0-3)	EMS (min)
				Patient	Physician				
Bresnihan, *et al.* 1998. [102;107] (0560)			(0-1)	(0-4)	(0-4)				
24 week data.[a] *(unadjusted)*									
Placebo	25.6 ± 10.3	32.8 ± 14.1	0.62 ± 0.2	3.0 ± 0.5	3.0 ± 0.4	4.2 ± 4.2	47 ± 30	1.5 ± 0.6	127 ± 92
Anakinra 30mg/day	26.2 ± 9.9	33.4± 13.5	0.62 ± 0.2	3.1± 0.5	3.1 ± 0.4	4.1 ± 3.7	49 ± 27	1.5± 0.6	138 ± 102
Anakinra 75mg/day	26.2 ± 10.2	35.7± 14.4	0.65 ± 0.2	3.1 ± 0.5	3.1 ± 0.5	4.2 ± 3.8	53 ± 31	1.6 ± 0.7	138 ± 109
Anakinra 150mg/day	26.6 ± 9.5	35.2± 13.5	0.63± 0.2	3.1 ± 0.5	3.1 ± 0.4	4.0 ± 4.0	49 ± 30	1.6 ± 0.7	133 ± 101
Study 960182 [103;108]			(0-100)	(0-4)	(0-4)				
12 week data.									
Placebo	25.1 ± 10.2	35.8 ± 13.0	65.6 ± 16.0	3.2 ± 0.5	3.3 ± 0.5	4.2 ± 3.9	47 ± 27	1.6 ± 0.7	136 ± 84
Anakinra 2.5mg/day	22.6 ± 10.1	32.4 ± 13.4	62.5 ± 18.5	3.1 ± 0.5	3.0 ± 0.4	3.1 ± 3.3	45 ± 26	1.7 ± 0.5	124 ± 92
Anakinra 10mg/day	24.0 ± 10.2	32.1 ± 11.6	56.3 ± 18.5	3.0 ± 0.5	3.1 ± 0.4	2.7 ± 2.9	40 ± 21	1.6 ± 0.6	132 ± 94
Anakinra 30mg/day	23.7 ± 9.6	32.4 ± 12.7	55.4 ± 18.8	3.1 ± 0.4	3.1 ± 0.4	2.8 ± 4.3	41 ± 27	1.5 ±0.7	117 ±83
Cohen, et al. 2002 [104;109](0180)			(0-100 scale)	(0-100 scale)	(0-100 scale) 56.7 ± 18.5				
24 week data									
Placebo + MTX alone	18.4 ± 9.8	28.1 ± 13.9	52.5 ± 22.2	52.6 ± 21.5	55.7 ± 19.2	2.0 ± 2.6	36 ± 28	1.4 ± 0.6	140 ± 113
Anakinra 0.04mg/kg/day + MTX	18.8 ± 8.7	23.9 ± 11.4	46.4 ± 20.9	47.6 ± 21.2	61.2 ± 17.6	2.2 ± 3.46	37 ± 23	1.4 ± 0.6	129 ± 90
Anakinra 0.1mg/kg/day + MTX	18.3 ± 9.2	25.9 ± 14.8	51.6 ± 22.4	51.1 ± 21.5	60.1 ± 18.5	1.6 ± 1.6	38 ± 25	1.5 ± 0.7	117 ± 91
Anakinra 0.4mg/kg/day + MTX	19.1 ± 9.2	27.1 ± 13.0	51.2 ± 21.3	50.4 ± 19.3	53.6 ± 17.0	2.1 ± 2.5	37 ± 26	1.5 ± 0.6	120 ± 91
Anakinra 1.0mg/kg/day + MTX	17.6 ± 8.8	22.0 ± 12.9	47.5 ± 22.8	47.5 ± 21.5	55.8 ± 18.5	1.6 ± 2.3	37 ± 25	1.3 ± 0.6	134 ± 99
Anakinra 2.0mg/kg/day + MTX	17.4 ± 8.1	24.6 ± 12.8	54.6 ± 21.4	51.2 ± 21.7		2.0± 2.6	35 ± 21	1.3 ± 0.6	143 ± 98
Cohen, et al. 2001 [105;110](0145)			(0-100)	(0-100)	(0-100)				
24 week data									
Placebo + MTX	20 ± 10.2	24.5 ± 13.1	55.7 ± 20.4	52.3 ± 19.8	57.0 ± 18.4	2.6 ± 2.6	43 ± 22	1.32 ± 0.6	111 ± 99
Anakinra 100mg/day + MTX	20.1 ± 11.7	26.8 ± 15.7	59.2 ± 21.6	53.2 ± 22.1	57.4 ± 18.7	2.7 ± 2.6	42 ± 22	1.36 ± 0.6	102 ± 84
Fleischman, et al. 2001 [106;111] *(0757)*									
24 week data									
Placebo + current DMARD regimen	18.3 ± 11.7	22.6 ± 14.5	Not reported	Not reported	Not reported	2.7± 3.3	Not reported	Not reported	Not reported
Anakinra 100mg/day + current DMARD treatment	18.8± 11.9	22.6 ± 14.7				2.7± 3.3			

[a] Based on modified ITT population n= 468. Four patients (2 placebo, 1 anakinra 75mg/day, 1 anakinra 150mg/day) had no post baseline assessment and were excluded form the analysis

Table 6 : Mean (SEM) change in measures of disease activity from baseline

STUDY	SJC 0-66	TJC 0-68	Pain score patient	Global score		CRP (mg/dl)	ESR (mm/hr)	HAQ (0-3)	EMS
				Patient	Physician				
Bresnihan, *et al.* 1998[102;107] (0560) *24 week data.*[a] *(unadjusted)*			(0-1cm)	(0-4)	(0-4)				
Placebo	-5.7 (0.9)	-5.2 (1.4)	-0.05 (0.03)	-0.5 (0.09)	-0.6 (0.08)	-0.4 (0.28)	+1 (2)	0.0 (0.04)	-14 (10)
Anakinra 30mg/day	-7.9 (1.2)	-8.6 (1.3)	-0.13 (0.03)*	-0.7 (0.09)	-0.9 (0.08)*	-1.3 (0.25)#	-9 (2)τ	-0.2 (0.05)*	-36 (10)
Anakinra 75mg/day	-6.8 (1.0)	-9.3 (1.3)	-0.12 (0.03)	-0.8 (0.09)	-0.9 (0.09)*	-1.0 (0.31)#	-8 (2)τ	-0.2 (0.04)*	-55 (11)#
Anakinra 150mg/day	-9.5 (0.9)#	-11.9 (1.2)τ	-0.17 (0.03)τ	*-0.9 (0.09)**	-1.0 (0.08)τ	-1.0 (0.49)#	-10 (3)τ	-0.3 (0.06)τ	-48 (10)
Study 960182[103;108] *12 week data.*[b]									
Placebo	-6.8 (1.7)	-11.4 (2.4)	-21.5 (4.3)	-1.0 (0.15)	-1.20 (0.13)	0.02 (0.19)	-2 (3)	-0.33 (0.09)	-55 (14)
Anakinra 2.5mg/day	-3.0 (1.5)	-7.2 (2.1)	-14.7 (3.8)	-0.8 (0.14)	-0.72 (0.12)	-0.01 (0.17)	1 (3)	-0.30 (0.08)	-26 (13)
Anakinra 10mg/day	-6.3 (1.5)	-9.7 (2.1)	-11.9 (3.8)	-0.9 (0.14)	-0.92 (0.12)	-0.06 (0.17)	-5 (3)	-0.09 (0.08)	-25 (13)
Anakinra 30mg/day	-6.4 (1.7)	-12.0 (2.4)	-12.9 (4.4)	-0.9 (0.16)	-0.82 (0.14)	0.01 (0.19)	-2 (3)	-0.21 (0.09)	-32 (15)
Cohen, et al. 2002[104;109](0180) *24 week data*[c]			(0-100)	(0-100)	(0-100)				
Placebo + MTX alone	-4.2 (1.0)	-8.3 (1.5)	-2.6 (3.1)	-3.6 (3.0)	-14.1 (2.9)	-0.19 (0.34)	-4 (2)	-0.15 (0.07)	-50 (12)
Anakinra 0.04mg/kg/day + MTX	-5.0 (0.9)	-6.9 (1.4)	-3.8 (2.9)	- 5.3 (2.8)	-11.5 (2.6)	0.15 (0.30)	-4 (2)	-0.25 (0.07)	-45 (11)
Anakinra 0.1mg/kg/day + MTX	-5.7 (1.0)	-7.9 (1.5)	-12.3 (3.1)	-12.4 (3.0)	-20.3 (2.9)	-0.06 (0.35)	-10 (2)	-0.33 (0.07)	-63 (12)
Anakinra 0.4mg/kg/day + MTX	-6.7 (0.9)	-9.7 (1.4)	-8.9 (3.0)*	-8.1 (2.9)*	-20.4 (2.8)	-0.74 (0.33)	-12 (2)#	-0.24 (0.07)	-41 (11)
Anakinra 1.0mg/kg/day + MTX	-6.3 (0.9)	-8.3 (1.4)	-12.9 (3.0)*	-13.8 (2.9)*	-22.3 (2.8)*	-0.77 (0.32)	-12 (2)#	-0.37(0.07)*	-74 (11)
Anakinra 2.0mg/kg/day + MTX	-7.6 (1.0)*	-11.2 (1.6)	-22.8(3.3)τ	-20.4 (3.2)τ	-24.5 (3.1)*	-0.77 (0.38)	-15 (3)#	-0.51 (0.07)τ	-82 (13)
Cohen, et al. 2001 [105;110](0145) *24 week data*[d]			(0-100)	(0-100)	(0-100)				
Placebo + MTX	-6.5 (0.6)	-8.7 (0.9)	-11.7 (1.8)	-8.9 (1.7)	-20.1 (1.5)	-0.10 (0.04)	-6 (1)	-0.18 (0.03)	-36 (6)
Anakinra 100mg/day + MTX	-6.8 (0.6)	-12.0 (0.9)#	-19.0 (1.7)#	-17.7 (1.6)τ	-25.2 (1.5)*	-0.51 (0.03)τ	-16 (1)τ	-0.29 (0.03)*	-48 (6)
Fleischman, et al. 2001[106;111] *(0757)24 week data* Placebo + DMARD Anakinra 100mg/day + DMARD	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported

[a] Based on modified ITT population n= 468. Four patients (2 placebo, 1 anakinra 75mg/day, 1 anakinra 150mg/day)had no post baseline assessment and were excluded from the analysis

[b] ITT analysis using least squares mean obtained from repeated measures mixed model adjusted for centre and baseline value, with the exception of HAQ outcome data which are provided for the completer subset only.

[c] Least squares mean obtained from repeated measures mixed model adjusted for study centre and baseline variable

[d] Adjusted mean and SE estimated by EMEA based on repeated measures mixed model adjusted for study week, treatment by study week interaction, centre and baseline value

* $p<0.05$ vs placebo # $p\leq 0.01$ vs placebo τ $p\leq 0.001$ vs placebo

Table 7: Percentage of patients showing ACR response and %age discontinuing therapy

Study & Intervention	ACR20	ACR50	ACR70	DRUG CESSATION		
				Any reason	Lack of efficacy	Toxicity
Bresnihan, *et al.* 1998. [102;107] (0560) *24 week data.*[a]						
Placebo	27	7	1	26	20	4
Anakinra, 30mg/day	39*	17*	4	20	13	4
Anakinra 75mg/day	34	11	1	19	12	6
Anakinra 150mg/day	43*	17*	1	24	9	9
Study 960182[101;103;108] *12 week data.*						
Placebo	43	13	6.7	10	0	7
Anakinra 2.5mg/day	26	2.4	0	19	7	7
Anakinra 10mg/day	28	7.5	0	7.5	2.5	2.5
Anakinra 30mg/day	34	6.9	0	10	3	7
Cohen, et al. 2002[104;109](0180) *24 week data*						
Placebo + MTX alone	23	4	0	19	7	4
Anakinra 0.04mg/kg/day + MTX	19	13	5	21	14	3
Anakinra 0.1mg/kg/day + MTX	30	20	7	16	10	1
Anakinra 0.4mg/kg/day + MTX	36	11	2	22	8	7
Anakinra 1.0mg/kg/day + MTX	42*	24	10	22	7	14
Anakinra 2.0mg/kg/day + MTX	35	17	7	26	6	15
Cohen, et al. 2001 [105;110](0145) *24 week data*						
Placebo + MTX	22	8	2	27	Not reported	9
Anakinra 100mg/day + MTX	38$^{\tau}$	17$^{\tau}$	6*	22		13
Fleischman, et al. 2001[106;111] *(0757)24 week data*						
Placebo + current DMARD regimen	Not reported	Not reported	Not reported	19	Not reported	6
Anakinra 100mg/day + current DMARD treatment				23		12

* $p<0.05$ $^{\tau}p\leq0.001$

3.2.4 Meta-analysis

Treatment with anakinra at doses in line with the licensed dose of 100mg/day showed a consistent clinical benefit in the trials included in this report. In order to get a summary measure of treatment effect data were pooled. We describe the methods and key findings below.

3.2.4.1 Methods

As this is a rapid review we restricted meta-analyses to six important measures of treatment. Three outcomes HAQ, patient global assessment, and swollen joint counts, which reflect physical disability, patient-centred outcomes and physician assessment of joint disease respectively, were reported as continuous data. Three other outcomes, the ACR20, ACR50 and ACR70, which are presented as binary data and which represent an overall measure of treatment effect were also analysed. The primary analysis pooled results from the latest follow up data available for the blinded, randomised, controlled period of each trial (24 weeks for all studies with the exception of 0182 where data are presented at week 12).

We pooled results for trials where anakinra (with or without methotrexate) was compared to placebo. Pooled results for use in combination with methotrexate (licensed indication) are also presented. For the dose ranging trials (0560, 0180) a chi-squared test for trend was undertaken for the ACR endpoint based on the aggregated data. Since individual patient data were not available for the disease activity endpoints a test for trend could not be undertaken since group data may be subject to the ecological fallacy*. Given that the test for trend on the ACR 20, 50 and 70 endpoints suggested that there may be a dose response, the doses closest to the licensed dose were pooled (75mg and 150mg for study 0560, 1.0 and 2.0mg/kg/day for study 0180). However all data should be considered relevant. A sensitivity analysis including all data is therefore also reported.

Where possible, the SD was taken directly from the reported results or derived from the SEM where used. Where an outcome was reported on the same scale the results are presented as a weighted mean difference (WMD).

A fixed effects model was used since statistical heterogeneity was not demonstrated across the trials.

To pool outcomes which use continuous data we used the final result not %age change from baseline. More estimates of variability were available in this way.

3.2.4.2 ACR Improvements

Licensed dose analysis
Pooled analyses for ACR improvements, (at or around the licensed dose of anakinra, based on n=1007) are shown in Figure 2, page 54, Figure 3, page 55 and Figure 4, page 56 as both

*The ecological fallacy is the attribution of group level associations (e.g. from aggregated trial data or countries) to the individuals that constitute the group.

relative risk (RR) and risk difference (RD). A clear treatment effect is evident for ACR20 but effect on the more rigorous endpoints of ACR50 and ACR70 is much smaller.

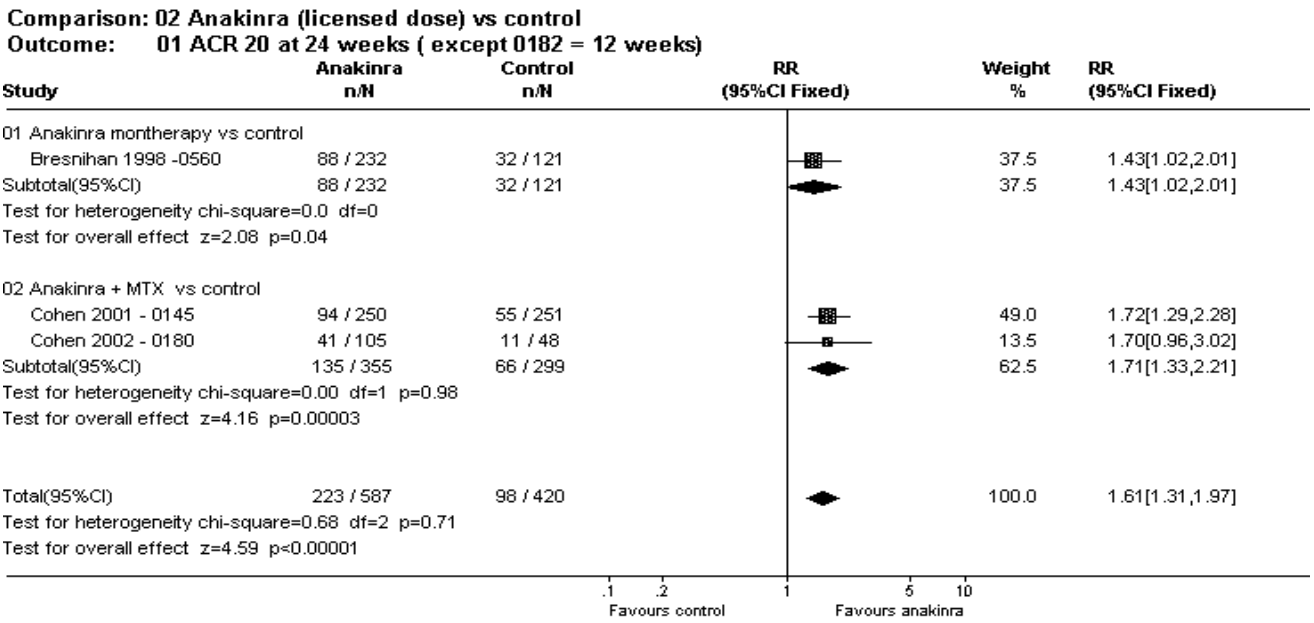
Clinical effectiveness, when expressed in terms of RR of achieving an improvement in ACR, increases with a higher hurdle, such that RR of achieving an ACR20 with anakinra was 1.6, whilst RR of achieving ACR70 was around 3, consistent with treatment effect. However, effectiveness expressed as a risk difference decreases, reflecting the much lower prospect of achieving an ACR50 or ACR70 with placebo. The number needed to treat (NNT) to achieve an ACR20 response was 7 (95%CI 5 to 11), NNT for ACR50 was 11 (95% CI 8 to 20) and the NNT for ACR70 was 33 (95% CI 20 to 100). Both the ACR50 and ACR70 are believed to be clinically very significant.

For the subset of patients enrolled in trials who received anakinra (at or around the licensed dose) in combination with methotrexate (based on n=654), the NNT to achieve an ACR 20 response was 6, ACR 50 was 9 and ACR 70 was 20 .

All dose analysis
When ACR endpoint data for all doses of anakinra evaluated in clinical trials are pooled (based on n=1429), the NNT to achieve an ACR20 response increases to 9 (95% CI 6 to 17) and for ACR 50 increases to 13 (95% CI 9 to 25). A statistical benefit in terms of ACR 70 response is no longer apparent.

Figure 2 : Anakinra (licensed dose) vs placebo result at end of trial - ACR20

Relative Risk



Risk difference

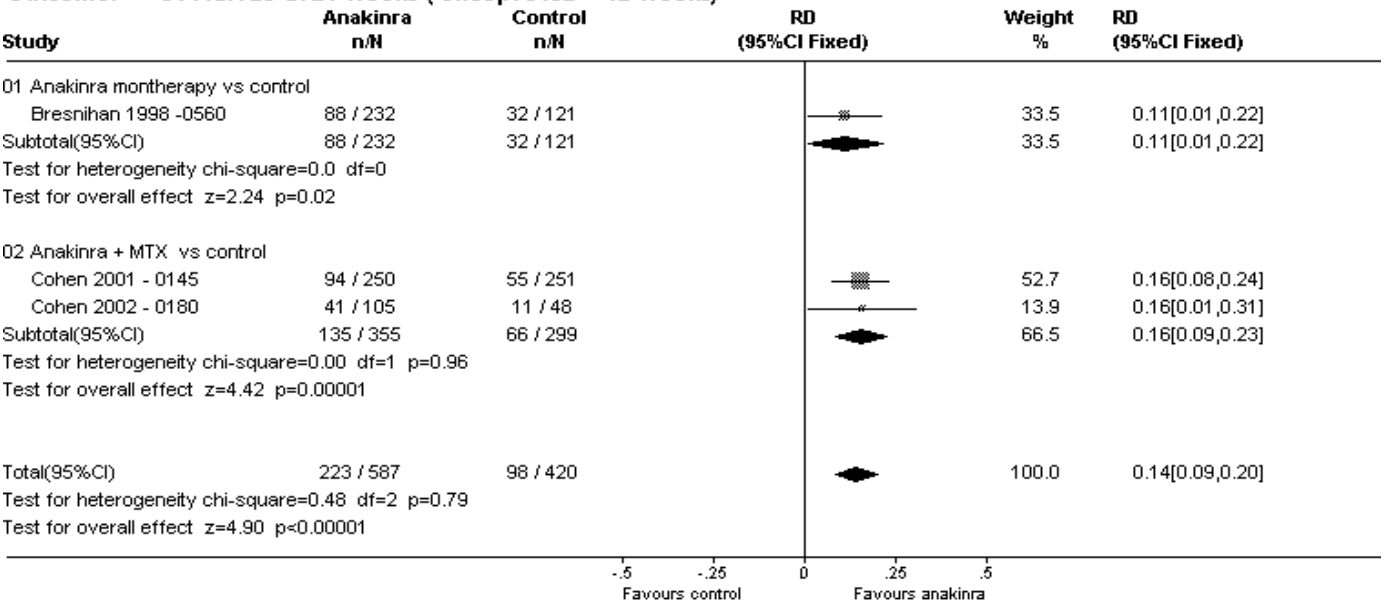
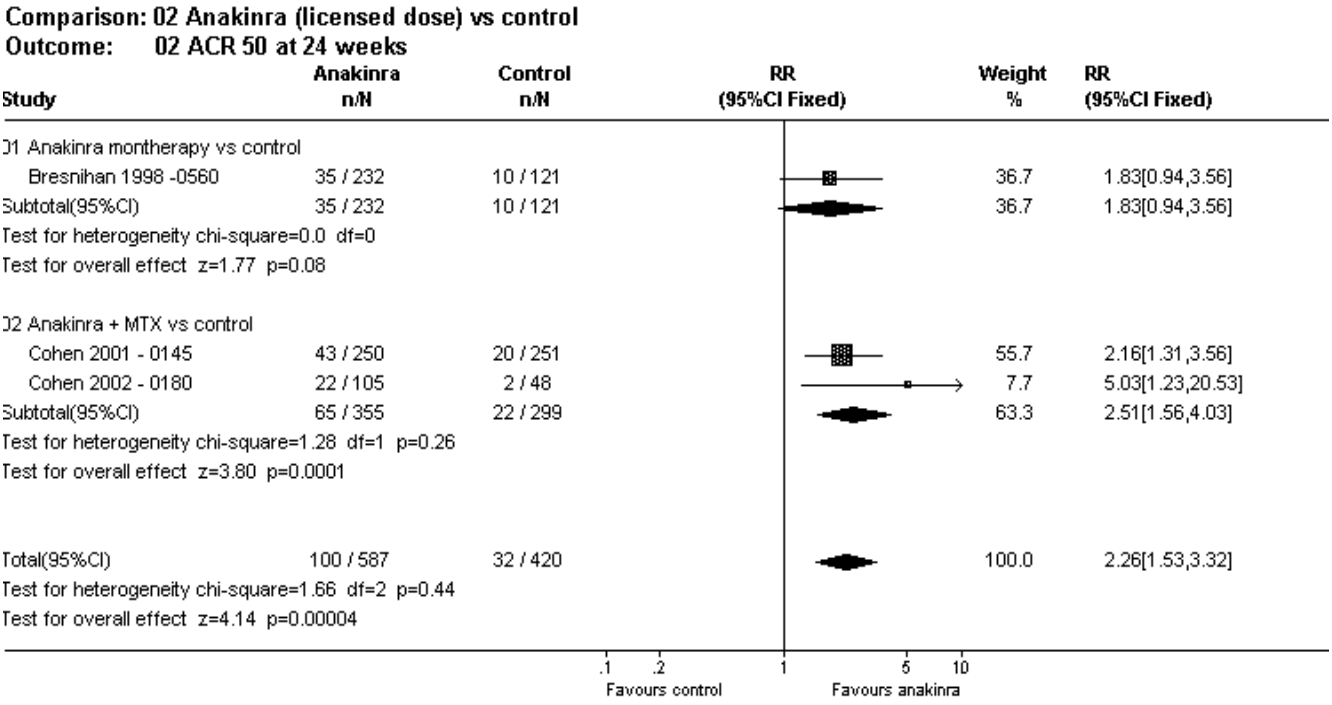


Figure 3 Anakinra (licensed dose) vs placebo result at end of trial - ACR50

Relative Risk



Risk difference

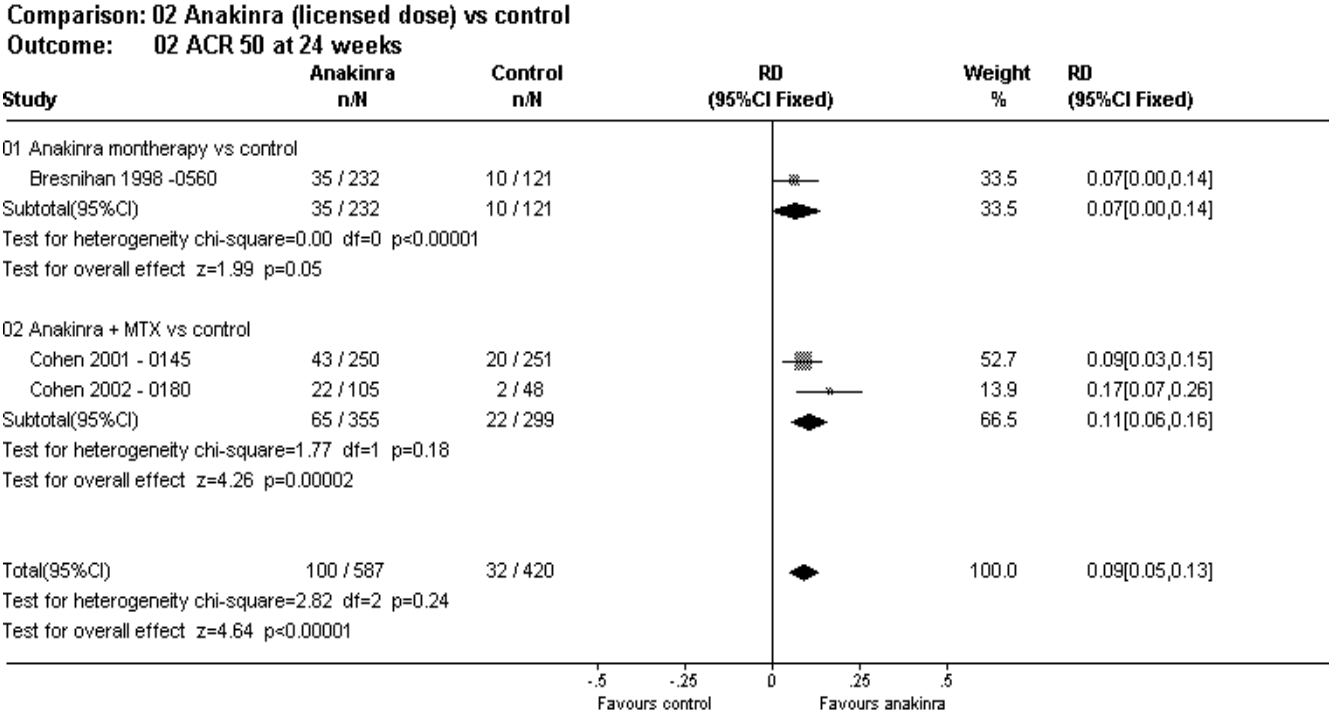
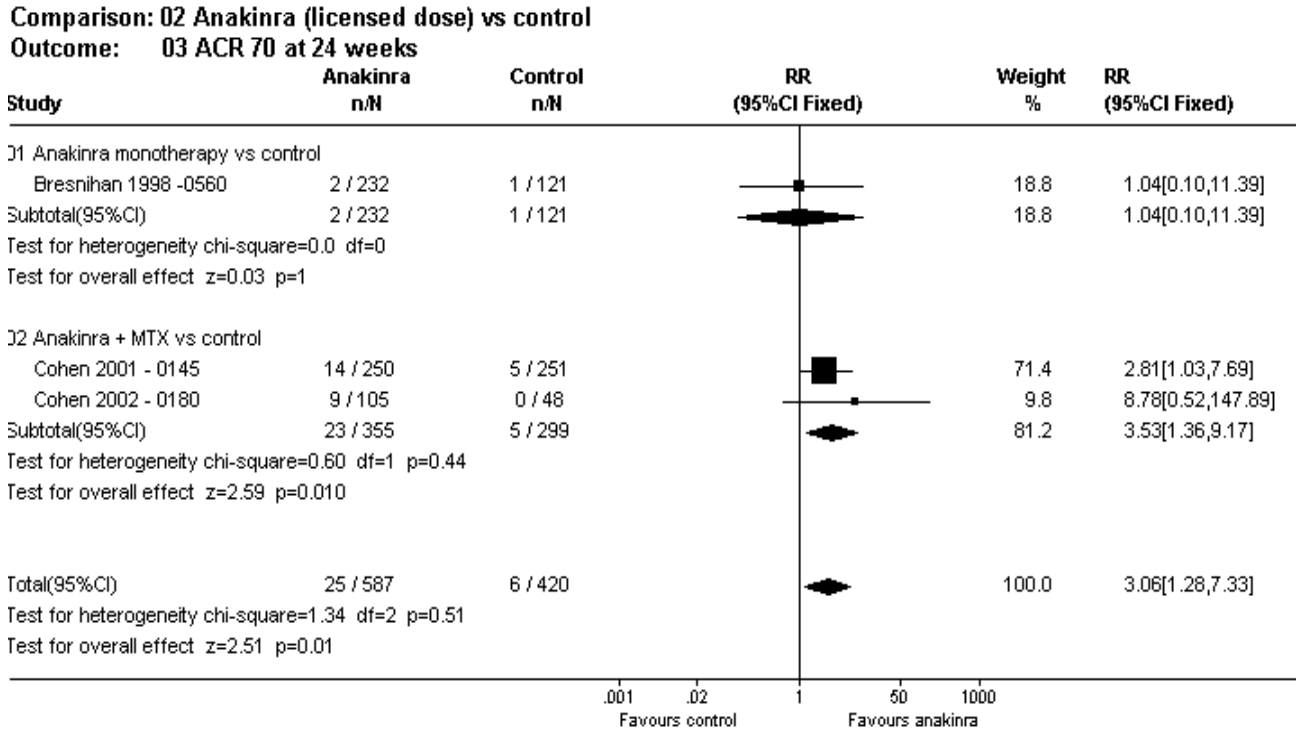
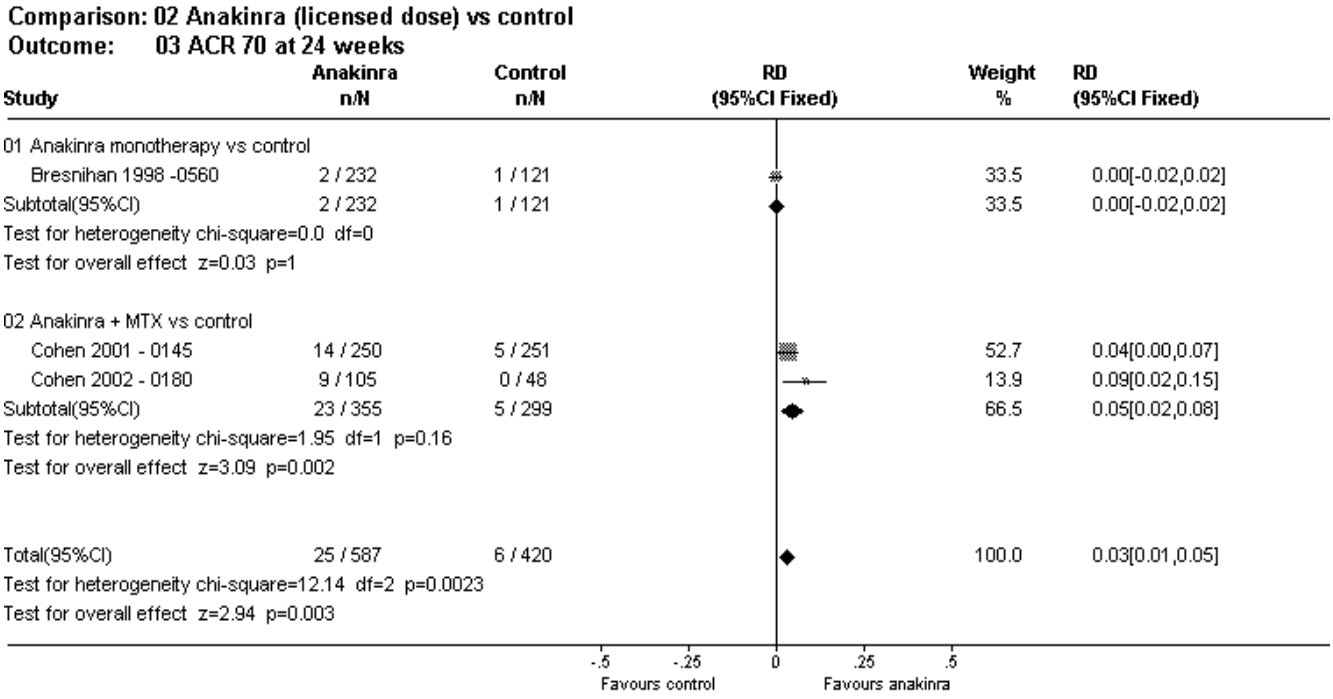


Figure 4 Anakinra (licensed dose) vs placebo result at end of trial - ACR70

Relative Risk



Risk difference



Sensitivity analysis considering study 0757

For any decision we make there will always remain some uncertainty and variability in the data that inform the decision. A key role of decision analytic modelling is, not only to obtain the best estimate based on current knowledge, but importantly, to investigate the consequences of plausible estimates concerning the uncertainties.

Trial 0757 had less restrictive inclusion criteria, to reflect the characteristics of people with RA, than the other trials (which use a more controlled patient population not representative of average clinical practice) and is therefore probably the most generalisable of all the trials to real life practice. Thus the findings of study 0757 are highly relevant to the Health Technology Assessment. Moreover over half the people who have received anakinra (1116 out of the 2146) were in this trial (of whom 77.4% completed the first six months) so a significant amount of trial data is missing. For these reasons trial 0757 should not be ignored.

The fact that the pharmaceutical company has declined to allow the effectiveness data for this trial into the public domain and their assertion that any statistical assessment of efficacy would be invalid, suggests to the authors of this report that the effectiveness in this pragmatic trial may have been less than in the earlier trials and probably did not reach conventional levels of statistical significance.

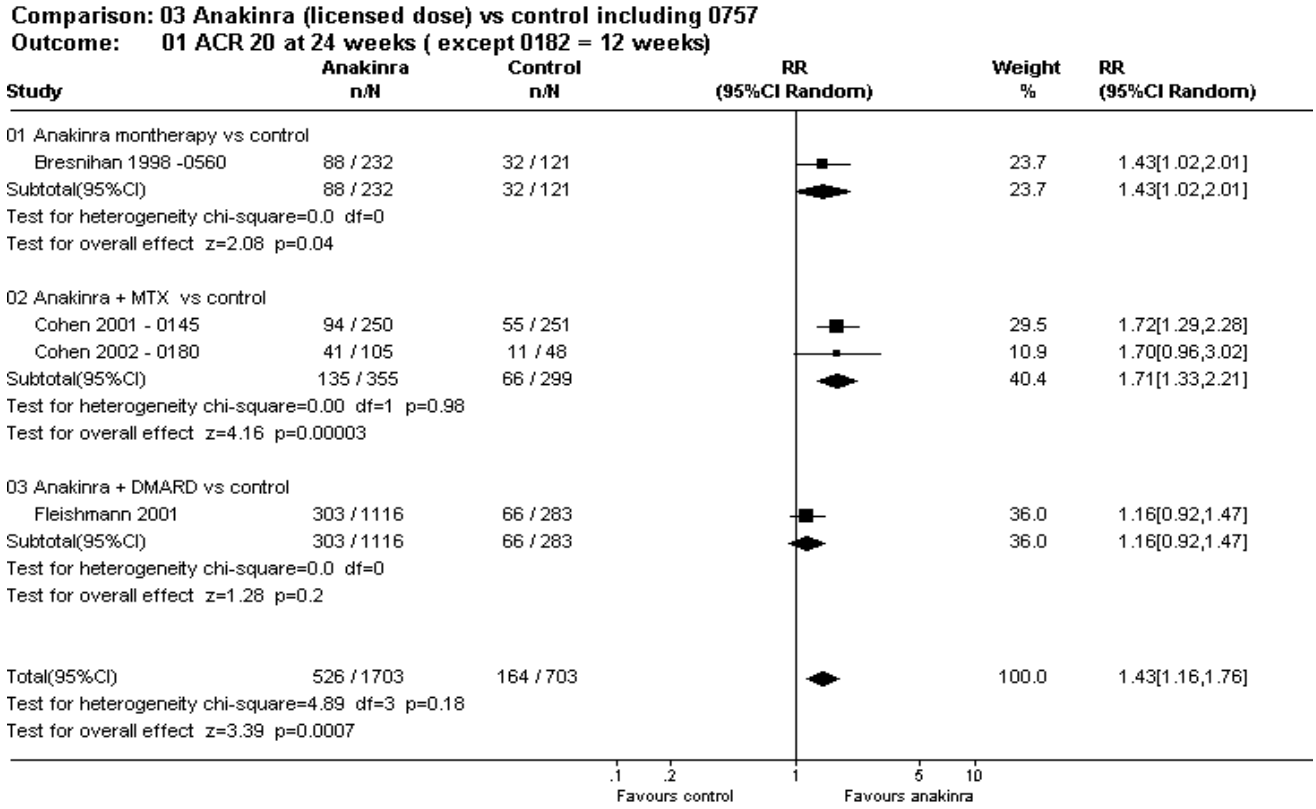
If the assumption were made that the withheld data showed no difference in effectiveness between the anakinra and placebo recipients, this would give the following combined estimate of effect for ACR 20 response: RR 1.39 (95% CI 1.03 to 1.87), RD 0.10 (95% CI 0.01 to 0.19). However, this figure almost certainly underestimates the effectiveness of anakinra seen in this trial as it is unlikely that, given the positive results from earlier trials, the result from 0757 would be completely null or negative.

However we think that the result was probably suggestive of benefit but failed to reach conventional levels of statistical significance. Based on the assumption that the results from this trial favour anakinra over placebo but the p-value of treatment difference was possibly of the order of $p< 0.1$ to $p<0.2$, we worked backwards to derive a plausible estimate of effectiveness for trial 0757. Of the 283 placebo patients, 66 were assumed to have an ACR20 response (paralleling the 23% response rate seen in the combined results for the placebo groups in earlier trials). We worked backward and calculated that a response rate of 303/1116 in the anakinra group would have given a two-sided $p<0.2$ or one-sided $p<0.1$.

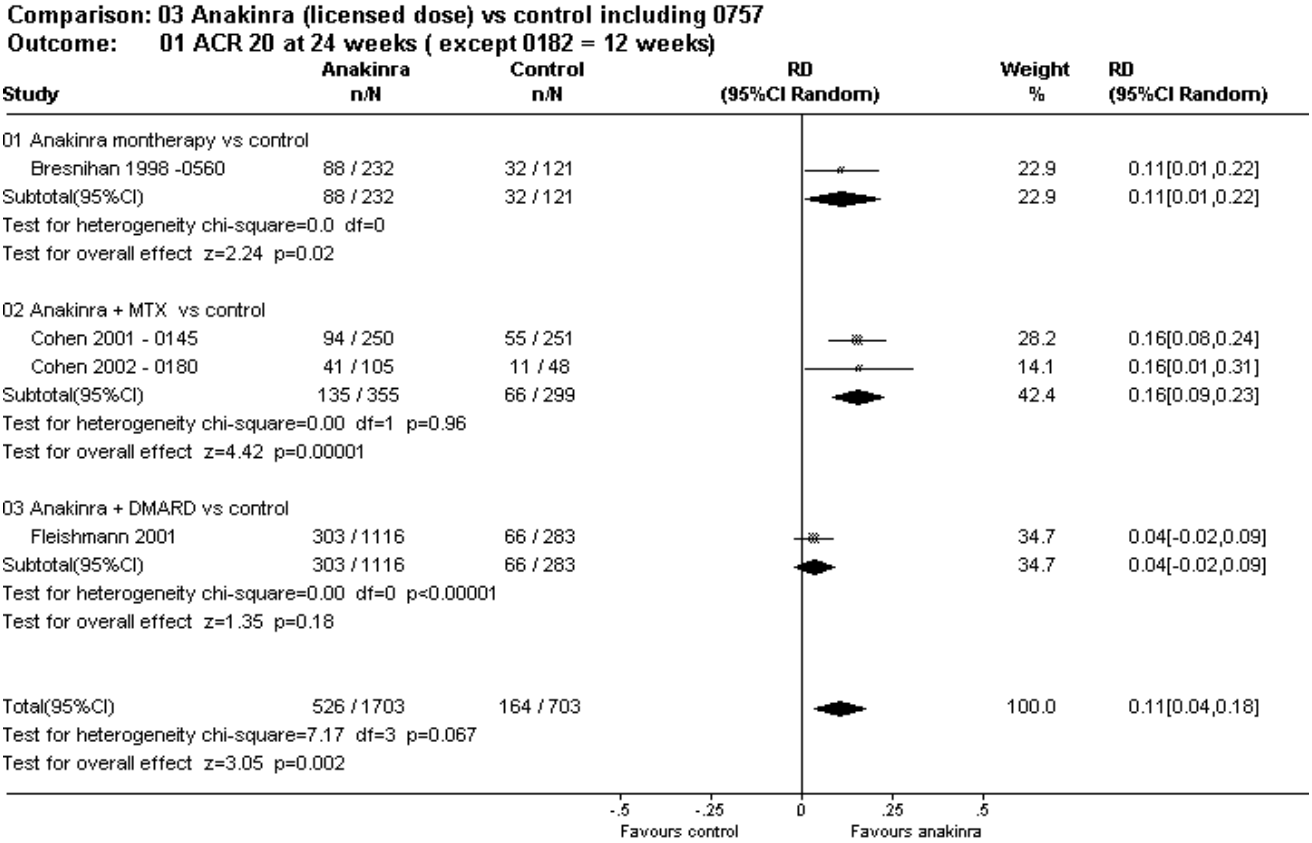
We combine this figure for trial 0757 with the data from the earlier trials to give our best summary estimate about anakinra's effectiveness (Figure 5, page 58). Given the fact that there is clinical heterogeneity in terms of different population characteristics, co-morbidities and co-medications in trial 0757 compared to earlier trials we combined 0757 with previous trials using a random effects model. This gives the following as the best summary estimate of effectiveness for the ACR 20 response; RR 1.43 (95% CI 1.16 to 1.76), RD 0.11 (95% CI 0.04 to 0.18), NNT 9 (95% CI 6 to 25).

Figure 5 Anakinra (licensed dose including study 0757) vs placebo, result at end of trial - ACR20

Relative Risk



Risk difference



3.2.4.3 HAQ Scores, patient global assessment, and swollen joint counts

The pooled result at the end of trials for HAQ scores for anakinra versus placebo gave a weighted mean difference of -0.18 (95% CI –0.12 to –0.24) with licensed doses (Figure 6, page 59) and –0.16 (95% CI –0.11 to –0.22) for all doses. The HAQ scale scores 0 for normal function and 3 for greatest disability, thus a reduction indicates improved function. Improvement in function was slightly less in the pooled analysis of trials which evaluated anakinra (licensed dose) in combination with methotrexate (WMD –0.14 95% CI –0.07 to –0.22)

Patient global assessment of disease activity, which indicates the patient's view of how the arthritis is doing, was scored in most trials on a scale of 0 (best) to 100 (worst). The weighted mean difference for anakinra at licensed dose compared to placebo was –10.4 (95% CI –6.3 to –14.4) at the end of the studies (Figure 7, page 60). This also represents the improvement seen with use in combination with methotrexate. The monotherapy trials 0560 and 0182 used a scale of 0 to 4 for patient assessment of disease activity and were not included in this meta-analysis. Whilst no effect was evident in the low dose study 0182, in study 0560 the direction of effect on patients global assessment of disease activity was consistent with the other trials, although the size of benefit is much smaller.

The swollen joint count at the end of studies was reduced by 1.5 (95% CI –0.38 to –2.68) in the anakinra (licensed dose) arms compared to placebo (Figure 8, page 60) and by 1.2 (95% CI –0.11 to –2.2) for all doses. Similar but slightly smaller benefit which was no longer statistically significant was evident with use in combination with methotrexate, reduction of 1.2 (95% CI 0.15 to –2.54).

Figure 6 HAQ: Anakinra (licensed dose) versus placebo

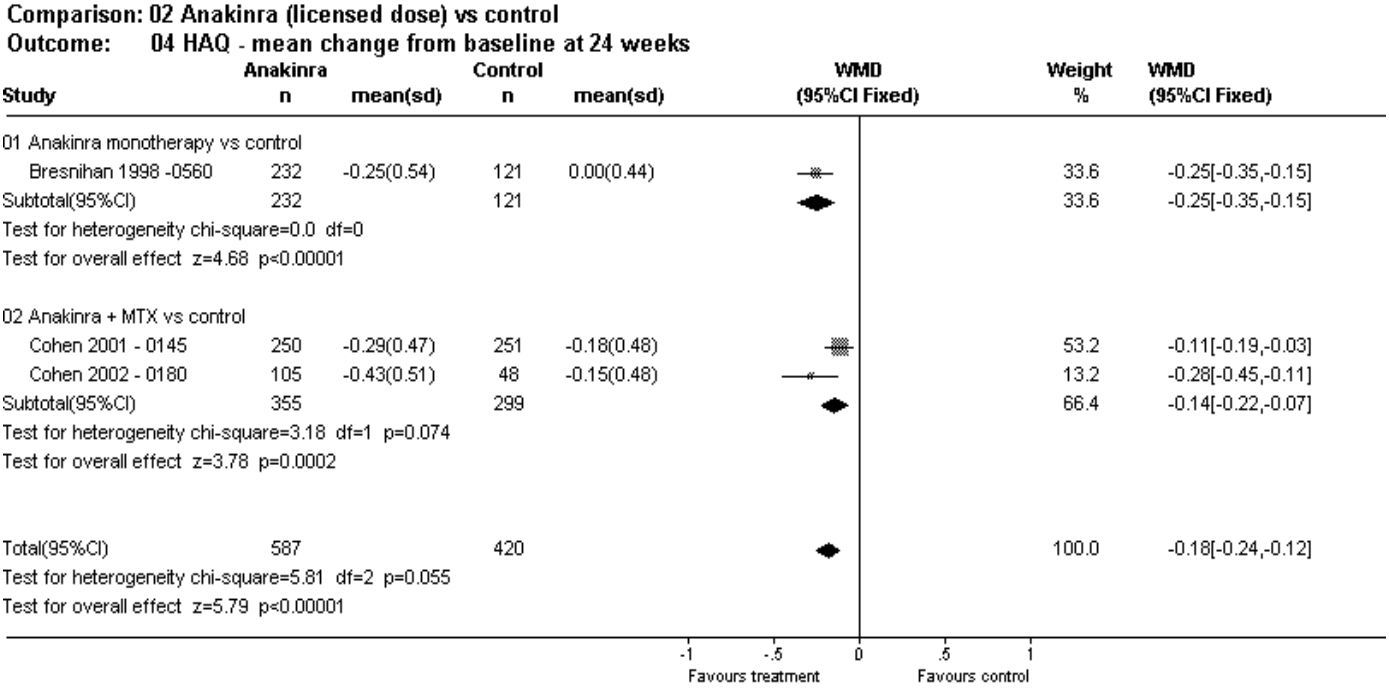


Figure 7 Patient global assessment: Anakinra (licensed dose) versus placebo

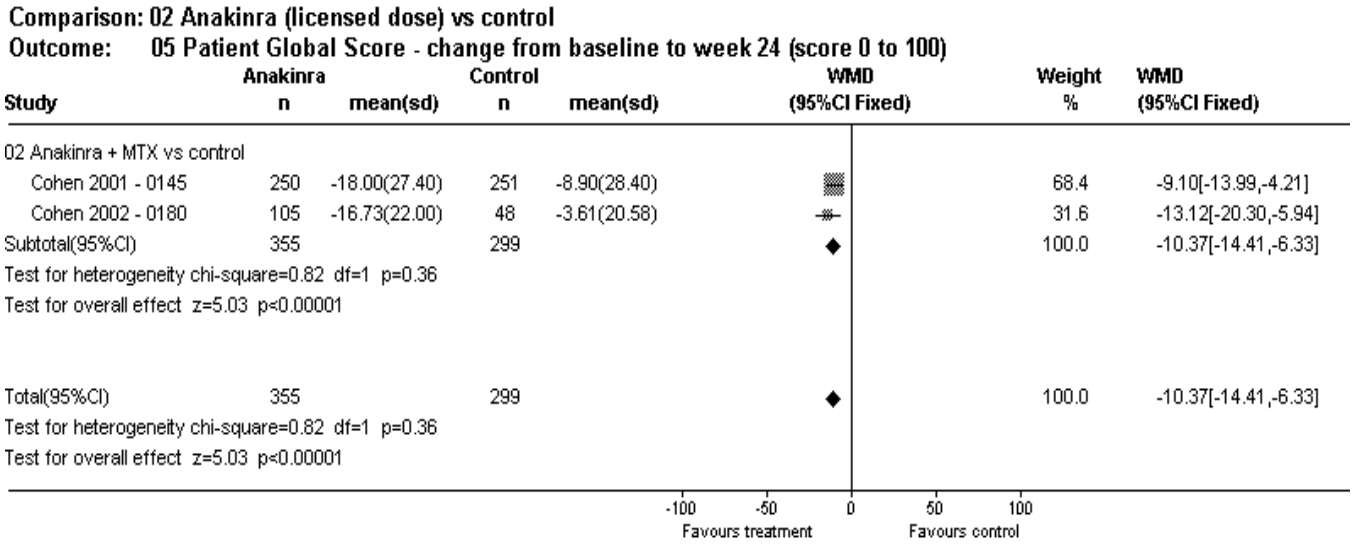
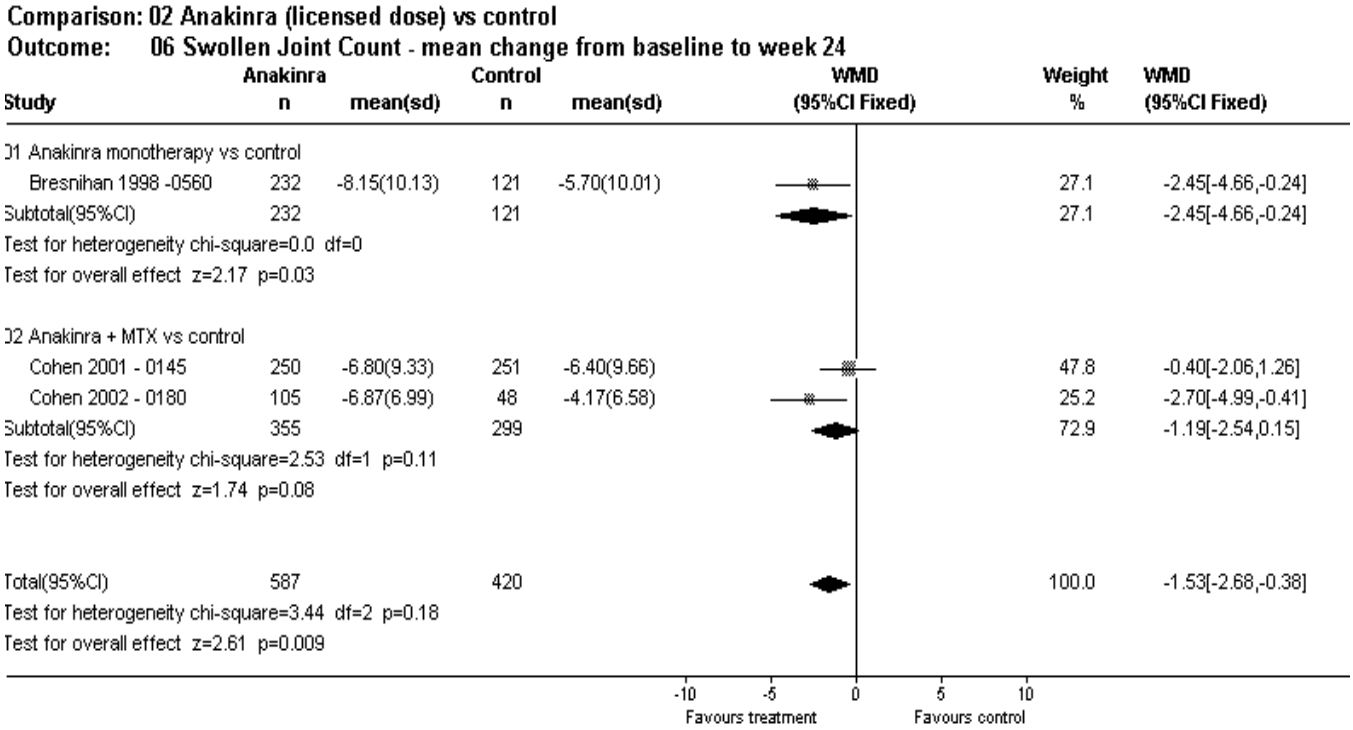


Figure 8 Swollen joint counts: Anakinra (licensed dose) versus placebo



3.2.5 Anakinra compared to other agents

The trial data clearly demonstrate that anakinra at the higher doses evaluated has a statistically significant effect, compared to placebo, on ACR 20% response rates in patients with RA. However, no trials have directly compared anakinra head-to-head with another DMARD or more specifically another biological modifier. In trials where patients continued with methotrexate but were given additional treatment with anakinra or placebo, these were not regarded as a direct comparison of DMARD against anakinra.

In Europe anakinra is only licensed for use in combination with methotrexate. A number of trials with TNF inhibitors have evaluated use in combination with methotrexate. Direct comparisons between these classes of drugs have not been undertaken. When there is no direct comparison it has been demonstrated that the adjusted indirect method (which makes some adjustment for variability in prognostic factors at baseline across trials) may be used to obtain some evidence about the relative efficacy of competing interventions. Such indirect results should of course be interpreted with caution, since the estimate provided may differ from that obtained by direct comparison within randomised controlled trials. Nevertheless the adjusted indirect method can be useful in guiding clinical practice in the absence of direct comparisons between agents.[113]

Results from 4 clinical trials that evaluated different biological modifiers in combination with effective doses of methotrexate have now been published; two with anakinra [104;105], one with etanercept[114] and one with infliximab.[115] Table 8 compares the clinical responses in terms of ACR across these trials, for all treatment doses combined for the etanercept and infliximab studies and the 'licensed dose' for anakinra. This differentiation was made since for anakinra a dose response appeared to be evident across the doses evaluated. The response was measured at endpoint, 24 weeks for anakinra and etanercept and 54 weeks for infliximab.

Table 8: Adjusted Indirect comparison of anakinra with TNF inhibitors

Intervention	Risk Difference for ACR 20 response
TNF + MTX vs MTX alone[39]	0.37 (0.28 to 0.45)
Anakinra + MTX vs MTX alone [104]	0.16 (0.09 to 0.23)
Anakinra + MTX vs TNF + MTX	-0.21 (-0.32 to -0.10)

This indirect comparison suggests that anakinra may be significantly less effective at relieving the clinical signs and symptoms of RA, as measured by the ACR response criteria, than TNF inhibitors all used in combination with methotrexate. The divergence in benefit is particularly evident at the higher levels of ACR response, 50% & 70%.

For the adjusted indirect comparison to be valid, the key underlying assumption is that the relative efficacy of an intervention is consistent in patients included in different trials i.e. that the estimated relative efficacy is generalisable. For both TNF inhibitors and anakinra consistent benefit was seen across clinical trials, trials were of similar design, conducted in similar settings with similar sorts of patients and were of high quality. Diagnostic criteria are standard in most contemporary trials and inclusion and exclusion criteria can also be considered sufficiently similar. We therefore have no reason to ignore the finding of such an indirect comparison.

3.2.6 Adverse Effects – Summary and additional data

The safety data for anakinra are derived from 2,606 subjects with RA who have been exposed to anakinra in clinical trials, including 1,812 (1,379 ≥100mg/d) exposed for at least 6 months and 570 (237 ≥ 100mg/d) exposed for at least 1 year.[96] Safety for up to 4.5 years has been evaluated in 67 patients in the open label extension study of 0560. No new safety concerns arose over this time.

Published data on adverse effects are available from the American prescribing information, the SPC, the 4 clinical efficacy studies and the 6 month, double-blind safety study. Amgen also have safety data from over 12,000 patients in the post marketing setting. Adverse events reported in the trial programme are summarised in Table 9 below.

Table 9: Summary of Adverse Events reported in Clinical Trials with Anakinra (all doses)

Adverse event						
	Treatment	**0560**	**0182**	**0180**	**0145**	**0757**
% withdrawing due to AE	Control	4.1%	7%	4.1%	9%	6%
	Anakinra	6.6%	5%	7.8%	13%	11.5%
Individual events						
Deaths	Control	0%	0%	0%	0%	0.4%
	Anakinra	0%	0%	0%	0%	0.4%
Serious adverse events	Control	11.6%	6.7%	4.1%	3.2%	7.8%
	Anakinra	12.8%	6.3%	6.7%	4.4%	7.7%
Malignancy	Control	0	0%	1.4%	NR	1.8%
	Anakinra	1.1%	0%	0.3%	NR	0.4%
Injection site reactions	Control	25%	3%	28%	24%	33%
	Anakinra	54.5%	19.8%	48%	65%	73%
Any infection	Control	38%	13.3%	50%	25.9%	43.5%
	Anakinra	37%	13.5	48.4%	33.3%	41.2%
Serious infection	Control	0.8%	NR	1.4%	0.8%	0.4%
	Anakinra	1.7%	NR	1.7%	0.8%	2.1%
Neutropenia	Control	4%	0%	0%	NR	NR
	Anakinra	9%	0%	1.4%	NR	NR
Antibodies to Il-1Ra	Control	0%	0%	1.8%	NR	NR
	Anakinra	0.9%	5%	2.7%	NR	NR

Trial 0145 - interim data whilst the trial was ongoing. AE data are limited to avoid breaking the blinding of the trial.

Across the five randomised controlled trials, adverse events led to withdrawal from treatment in 6.7% control and 10.1% anakinra treated patients. The difference in withdrawal rates between control and anakinra were primarily the result of ISRs.

Deaths
Eighteen patients died whilst taking study medication (5 during double blind treatment and 13 during open label extension studies); 4 cancer, 3 infections, 5 cardiovascular events, 6 other. All but one of these deaths occurred in patients taking anakinra. A further patient died

37 days after discontinuing study drug (anakinra) from a condition which developed whilst on study medication.[103]

Serious adverse events (SAEs)
Serious adverse events were essentially defined as any event that represented a significant hazard to health. This encompassed events that were life threatening, permanently disabling, required or prolonged hospitalisation, resulted in death, or constituted cancer, congenital abnormality or overdose. The incidence of serious adverse events in each of the four trials presenting results was similar with control and active treatment; 6.5% vs 8% respectively across all four trials.

For trials 0560, 0182, 0180 and 0145 the number of SAEs was small and no meaningful conclusions can be drawn. No treatment specific trends were noted.

In trial 0757 whilst the incidence of SAEs was similar between the study groups, when analysed by body systems compared to control a higher proportion of anakinra treated patients suffered GI (<0.4% vs 1.8%) and respiratory (0.4% vs1.6%) events. No predominant GI event was evident, however the higher incidence of respiratory events could in part be accounted for by higher incidence of pneumonia. In contrast more patients on control suffered a serious musculoskeletal event 2.8% vs 2.5% with anakinra, predominantly RA.

Malignancies
Twenty two malignancies were reported across studies 0560, 0180 (and their open label extensions) and study 0757; 16 with anakinra treatment and 6 with control. No predominant type of malignancy was observed. A single malignancy, prostate cancer, was reported during the 6 month interim analysis of study 0145. Due to maintenance of the blind it is not known which medication this patient was receiving.

The incidence of malignancies within clinical trials was within the expected range. Follow up over the longer term is however required to fully evaluate the effects of anakinra on malignancy.

Injection site reactions (ISR)
These represent the most common and consistently reported treatment related adverse event associated with anakinra in clinical trials, being seen in over 60% patients who received therapeutic doses vs < 34% with control. Such ISRs resulted in withdrawal from treatment in up to 10% patients treated with anakinra and up to 3% treated with control.

Table 10 Reports of and withdrawals due to injection site reactions across clinical trials

Trial		Control	Anakinra								
			30mg	75mg	150mg	0.04 mg/kg	0.1 mg/kg	0.4 mg/kg	1.0 mg/kg	2.0 mg/kg	100mg
0560	ISR withdrawals	25% 2%	50% 0.8%	73% 3%	81% 5%						
0182	ISR withdrawals	3% 0%	35% 0%								
0180	ISR withdrawals	28% 2.7%				19% 0%	38% 0%	56% 1.3%	64% 6.8%	63% 9.7%	
0145	ISR withdrawals	24% 0.8%									65% 8.4%
0757	ISR withdrawals	33% 1.4%									73% 7.1%

These reactions were characterised by erythema, ecchymosis, inflammation and pain. Such reactions were usually reported as mild to moderate occurred within the first 4 weeks of treatment and typically lasted for 14-28 days. The frequency of ISRs was seen to increase with increasing doses of anakinra across the trials.

Infections
The overall incidence of infections in each trial was comparable across the control and active treatment groups ranging from 26% to 50% (refer to Table 9, page 62).

URTIs, bronchitis, influenza-like symptoms and UTIs were the most commonly reported infections in trials 0560, 0180 and 0757 (Table 11, page 64). Sinusitis was also documented as a common event in all but trial 0560. These data are not available for studies 0182 and 0145. For the interim analysis of 0145 it is stated in the trial report that respiratory infections were most common (15.5% with control vs 21.2% with anakinra, no further details given).

Table 11: Incidence of commonly occurring infections for studies 0560, 0180 & 0757

Infection	**CLINICAL TRIAL**					
	0560		**0180**		**0757**	
	Control	Anakinra	Control	Anakinra	Control	Anakinra
URTI	6.6%	7.1%	21.6%	17.1%	18.4%	13.3%
Sinusitis	1.7%	0.9%	14.9%	8.4%	6.0%	6.7%
Bronchitis	4.1%	2.6%	0%	3.2%	4.6%	3.4%
Influenza like symptoms	5.8%	5.7%	5.4%	6.1%	6.4%	5.8%
UTI	5.8%	3.4%	5.4%	5.2%	5.3%	4.6%

In the large safety study (0757) whilst the incidence of infections was similar across the two groups, when analysed by body system, the GI system showed a higher proportion of subjects with infections in the anakinra arm compared to control (5.0% vs 2.8%). [103] No individual type of infection or group of infections accounted for this difference.

Considering the subset of infections defined as serious. The incidence in study 0757 was increased with anakinra compared to control (2% vs 0.4%). The most common infections

were pneumonia, cellulitis and osteomyelitis. None of the 23 infections in patients on anakinra were fatal. All resolved with the exception of one case of osteomyelitis. The potential risk factors identified for the higher incidence of serious infections were corticosteroid use and possibly asthma. [103]

In studies 0560, 0180, 0182 & 0145 only small numbers of patients developed serious infections.

Neutropenia
Treatment with anakinra is associated with small reductions in the mean values for WBC count and absolute neutrophil count (ANC). The incidence of neutropenia surprisingly is not reported for all trials. Trial protocols however required treatment to be withdrawn when WBC or ANC levels fell below pre-defined values.[116]

Across studies 0560 and 0180, 85 of 696 patients treated with anakinra (12%) developed neutropenia compared to 10 out of 195 treated with control (4%). For these figures neutropenia is defined as an increase of at least one grade of the neutropenia. Most of this neutropenia was mild.[103]

Withdrawal due to neutropenia was reported for 8 patients (1.1%) receiving anakinra and none receiving control in these trials. Time since initiation of anakinra treatment varied with about one third developing in the first 100 days and one third after 200 days of treatment. In all cases the ANC recovered on withdrawal of the drug. Only 1 case was associated with an infection.[103]

No data on neutropenia are provided for the large pragmatic safety study.

Antibodies to IL-1Ra
Limited data are available. In study 0560 of 454 patients who had baseline and follow up serum samples available 3 patients on anakinra developed positive reactions for anti-IL-1Ra antibody reactivity, at 2 or more follow up visits. None were observed in the control group. In study 0180 one of 57 screened patients administered control and 8 of 297 administered anakinra were seropositive for antibodies to IL-1Ra at some time during the study. Injection site reaction occurred in 7/8 seropositive patients given anakinra. No evidence of neutralising antibodies was detected.

4 ECONOMIC ANALYSIS

Summary of existing economic evaluations

- No fully published economic evaluations of anakinra in patients with RA were identified. Two abstract reports presented limited data.

Commentary on submitted model

- Markov model with six month cycle time
- There are problems associated with the structure of this model which makes its conclusion, that the ICER for anakinra is £16,545/QALY, unreliable

Summary of the Birmingham economic model

The Birmingham Rheumatoid Arthritis Model compares DMARD sequences of drugs, chosen to reflect current clinical practice, with and without anakinra, at different points in the DMARD sequence

The BRAM gives a base-case estimate of the ICER of anakinra of between £106,000/QALY to £604,000/QALY.

This model uses data from public domain trial results only. These trials recruited a highly selective patient population and may well overestimate the cost-effectiveness that anakinra would achieve in an average clinic population.

In the sensitivity analyses quite substantial variations were made in key parameters and ICERs were shown to be responsive. ICERs did not drop below £50,000/QALY in any univariate sensitivity analysis.

The BRAM produces an ICER for anakinra substantially higher than those for infliximab and etanercept. However, patients may respond to anakinra when they have not responded to other biologics, as these agents have a different mechanism of action. Thus anakinra may produce a clinically significant and important improvement in some patients that they could not otherwise have achieved.

4.1 Introduction

This section of the report has three components:

- a review of existing economic evaluations of the use of anakinra in RA
- a technical commentary on the decision-analytic models used in the economic analyses reported in the Amgen's submissions to NICE
- a description of the modelling and economic analyses of anakinra use in RA patients, undertaken by the authors.

4.2 Existing economic evaluations

There is extensive literature on the burden of illness and general costs associated with RA, which provides an indication of the substantial cost burden imposed on individuals and society as a result of the condition.[81;117-125] In addition, a number of published economic

analyses of drug therapies for use in RA were also identified, both relating to the use of NSAIDs for example, see Gabriel and colleagues[126] and DMARDs.[127-130]

No fully published economic evaluations of anakinra treatment for patients with RA were identified from the literature (refer to section 3.1.1 for methodology). Two abstract reports of economic evaluations, which considered use of anakinra in patients with RA, were identified.[131;132] These abstracts contained insufficient detail to justify reporting here at length. Hochberg and colleagues present a cost-minimisation analysis. This is based on ACR response from placebo controlled RCTs conducted with etanercept, infliximab and anakinra all in combination with MTX. Indirect comparison suggests that anakinra is associated with higher cost to achieve an ACR response than the TNF inhibitors. As discussed previously caution is advised when interpreting data from indirect comparisons.[131]

Brennan and colleagues developed a conceptual model of clinical pathways to compare therapeutic strategies; use of anakinra blind versus use in patients testing positive for IL-1A allele 2 (using outcome data from a preliminary study). The analysis suggested that there is the potential for a pharmacogenetic test to be cost effective in RA.[132]

4.3 Report on the Amgen model

Within their submission to NICE Amgen present an economic evaluation using a Markov model (see Appendix 7, page 96, for how this economic evaluation was scored using the checklist). The Amgen Markov model was based on the modelling structure used by Kobelt *et al*.[133;134] The Kobelt model classifies patients into six disease states by HAQ score. By allowing a separate set of transition probabilities for each time cycle within the model, the Kobelt model is able to fit any set of patient-level data to describe the progression over the period of follow-up of a study. This non-parametric approach has the advantage that it does not impose any structural assumptions on the data. However, it means that it is not obvious how to extrapolate time forward using the model. More importantly, the transition probabilities so fitted may be averages across heterogeneous groups of patients, in which case they would not have any meaning for particular patients. This would certainly be the case if the model were applied to a group of patients receiving a variety of different treatments.

The published form of the Kobelt model, with only six states for live patients, is not suitable for assessing the impact of a strategy of using drugs sequentially, either singly or in combination. The Amgen model overcomes this limitation to some extent by incorporating two sets of six "live" states, one set for patients on anakinra and one set for patients not on anakinra.

It is not at all clear what population is being modelled. The statements on pages 39-40 of the Amgen submission appear to contradict one another. Firstly the report states that the model is used to estimate the cost effectiveness:

> *"…in the treatment of patients with RA in whom conventional DMARDs are no longer effective."*

However then it talks about patients who fail anakinra being

> *"…maintained with conventional DMARDs. In addition, if treatment resulted in any adverse event that led to withdrawal from the treatment, the patient would be*

classified as a failure, and would be treated from then on with conventional DMARDs."

If anakinra is to be used as anything other than a "last resort" treatment, the patients not on anakinra will consist of a mixture of those still able to benefit from DMARDs and those not taking them. In this case it would not be appropriate to regard these as homogeneous groups, applying costs and transition probabilities to the groups as a whole. Thus, if it is to be coherent, the model should be interpreted as applying only to the choice of anakinra as therapy when all others have failed.

4.3.1 Technical aspects of the model

The model was supplied in two forms, one based on study 960180 (anakinra in combination with MTX) and one based on study 0560 (anakinra as monotherapy). The two forms have the same basic structure, but differ in the data used to populate the model. The model runs to a cycle length of 6 months.

4.3.2 Model Structure

Each version of the model compares two strategies, one involving anakinra and the other not. For the branch not involving anakinra, there are seven states: six live states and one representing death. Time-dependent transition probability matrices are used to determine the proportions of patients in each state at the end of each cycle. The first cycle uses the results of the appropriate study (960180 or 0560), but subsequent cycles use instead probabilities calculated from the Early Rheumatoid Arthritis Study (ERAS) data set.

For the branch involving anakinra, there are 13 states: six live states for remaining on anakinra, six live states for anakinra failures, and death. Transition probabilities from the failure states are as for the non-anakinra arm. For patients on anakinra, a probability of death is first applied; survivors may then remain on anakinra or not, and may change health state. The same transition matrices for health states are used for those who remain on anakinra and those who do not. The transition matrices for the first cycle are taken from 960180 or 0560 as appropriate. The second cycle probabilities are taken from 0564, and are the same in the two versions of the model (except for a difference in rounding in one case). For later cycles, the transition probabilities used are the mean of the probabilities in the previous two cycles.

There are several problems associated with this structure. These are detailed below. State numbers referred to here are for the six health states determined by HAQ score, ranging from state 1 (best; HAQ < 0.6) to state 6 (worst; HAQ 2.6 to 3.0). Many of the problems are inherent in the structure of the model as supplied; where it is possible to test an alternative by changing the values of variables used in the model, the effect of such changes is quoted below.

4.3.3 Overfitting

Values from the appropriate data sources appear to have been applied exactly, with no evidence of any attempt at smoothing or checking for consistency. For example, in trial 960180, the transition probability for the improvement from state 3 to state 1 is actually higher for placebo than for anakinra.

4.3.4 Different handling of death according to treatment

For patients still on anakinra, the probability of death is derived from UK death rates. However, for patients not on anakinra, death rates are included in the transition matrices derived from the ERAS data set. In all cases, there are zero probabilities for death recorded for many cycles. A common pattern is for non-zero probabilities to appear in alternate cycles only. This suggests that survival data was only available on an annual basis, but all deaths have been put into the same half of successive years.

4.3.5 Independence of transition with response status

For patients who are on anakinra at the start of a cycle, the transition probabilities for health states are exactly the same for those remaining on anakinra as for those quitting. It would be more reasonable to assume that those staying on anakinra would in general be in a better health state than those quitting the drug.

4.3.6 Calculation of transition probabilities after the first two cycles for anakinra patients

Transition probabilities for anakinra patients after the first two cycles are calculated as the mean of the probabilities for the previous two cycles. Applying this process repeatedly has the effect that the probability for a given transition converges towards a figure $\frac{1}{3}p + \frac{2}{3}q$, where p is the probability for the first cycle and q for the second cycle. This does not seem to be a sensible way of calculating these. The sensitivity analysis provided includes the effect of fixing the probabilities for later cycles to remain at the value for the second cycle. This is done separately for the probability of remaining on anakinra, and for the transition probabilities between health states for those remaining on anakinra. The effect of each of these changes is to increase the ICER slightly. In the model based on trial 960180, the ICER increases from £16,545 to £17,561 if the probability of remaining on anakinra is fixed after the second cycle. It increases from £16,545 to £17,399 if the transition probabilities between health states are similarly fixed. The combined effect of the two changes is not stated.

4.3.7 Patterns of zeros in the transition matrices

Because the studies from which the anakinra data were taken had very few patients in health state 6, there are many zero values in the transition matrices. The method used to project the probabilities has the effect that if the probability of a particular transition is zero in each of the first two cycles, it necessarily remains zero thereafter. This has the effect that in the model based on study 960180, it is possible to move from state 6 to state 3, but not 2 or 4, while in the model based on study 0560, it is possible to move from state 6 to state 2 or 4, but not to state 3.

As a measure of the significance of the above problem, if the initial population is amended by changing all the starting patients in state 6 to state 5, the ICER for the model based on study 960180 increases from £16,545 to £26,904.

4.3.8 Costing

Apart from the cost of anakinra, the costs for the model are based on costs for each health state. These costs include costs of DMARDs and associated monitoring for a substantial proportion of the patients in the data set from which they were derived. Such costs cannot be regarded as representative of costs for patients who are not taking DMARDs. If these costs are removed completely, the ICER for the model based on study 960180 decreases from £16,545 to £16,314. It can thus be seen that the effect of these costs on the model is not substantial.

4.3.9 Utilities

The model is based on utilities for each of the health states. The base-case utilities used are taken from applying the EQ-5D questionnaire to a group of patients. The numbers in each state ranged from approximately 25 to 40. The mean values for each group are used, and appear to be reasonable.

4.3.10 Sensitivity analysis

A number of one-way sensitivity analyses have been carried out. These include fixing transition probabilities for anakinra responders as described above. Additionally, a probabilistic sensitivity analysis was performed which varied the cost and utility estimates for the various health states in the model, but no other parameters. There are some minor problems with the way the distributions for utility scores were determined. However, the purpose of probabilistic sensitivity analysis is to represent all the uncertainty together. A probabilistic sensitivity analysis on a limited set of variables does not meet this purpose.

Crucial uncertainties which have not been tested include the following two. First, there is uncertainty in transition probabilities resulting from the very small numbers in certain states in the trials. Second, the model uses the same transition probabilities between health states for patients starting a cycle on anakinra, regardless of whether anakinra remains effective. The structure of the model does not allow this issue to be tested.

4.3.11 Conclusion

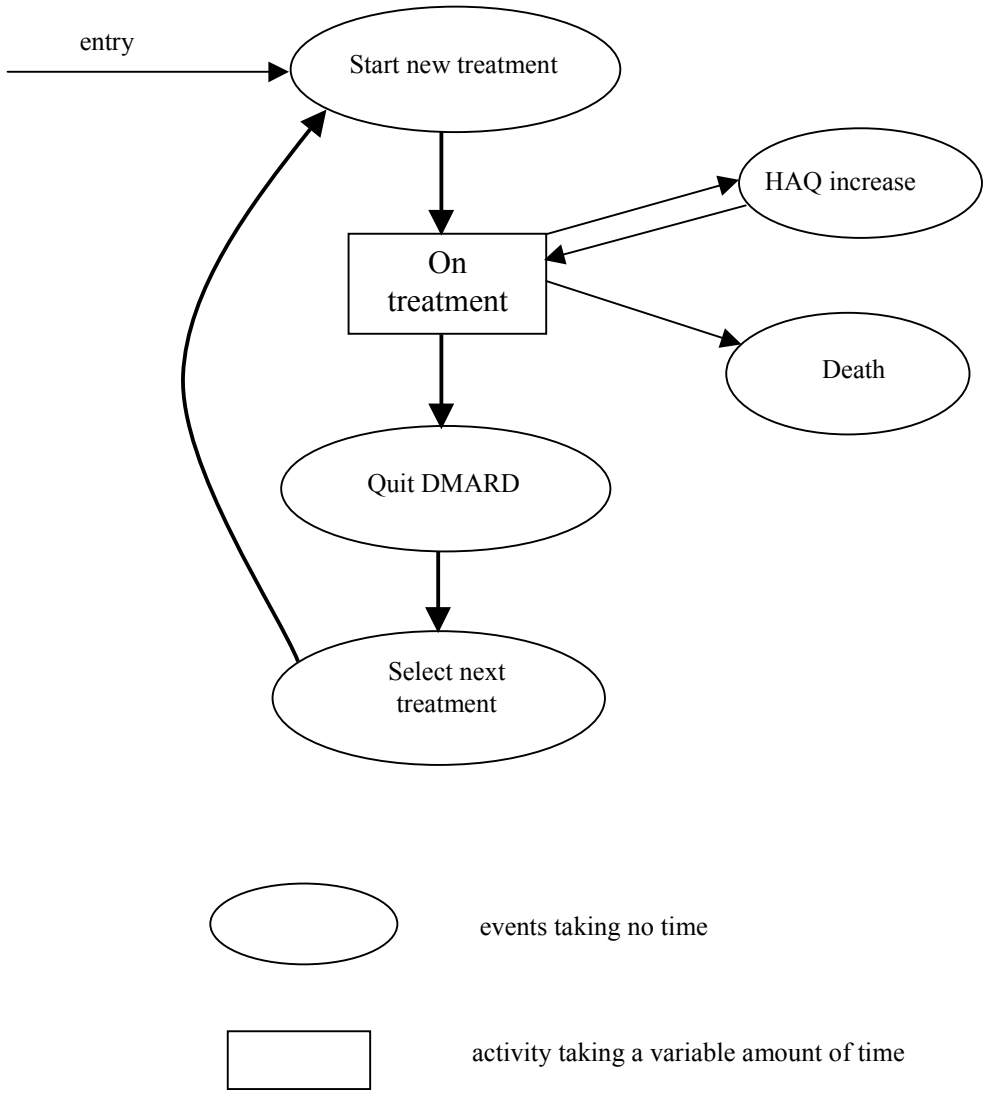
The results of the Amgen model must be treated with considerable caution.

4.4 Methods for Economic Analysis

The aim of this analysis is to assess the cost-effectiveness of adding anakinra to an existing treatment pathway for rheumatoid arthritis compared to the same pathway without anakinra. The costing perspective of the evaluation is NHS costs.

The economic analysis was conducted using the Birmingham Rheumatoid Arthritis Model (BRAM). This model is a revised version of a previous model used in the assessment of etanercept and infliximab.[39] The BRAM is an individual sampling model. A large number of virtual patient histories are simulated, costs and QALYs being accumulated as required. Full details of the means used to implement the model are to be found in a parallel report.[135] A complete description of the model structure is given below. The basic model structure is as in Figure 9, page 71

Figure 9 Basic structure of the model



Patients are assumed to follow a sequence of DMARDs, involving starting treatment, some time on the treatment, quitting the DMARD and selecting the next treatment. The pattern is then repeated for the next DMARD. Any patient surviving all the DMARDs moves on to palliation. Patients' HAQ scores are assumed to improve (decrease) on starting a DMARD; this improvement is lost on quitting the DMARD, which may be for reasons either of toxicity or loss of effectiveness. While on any treatment, patients' condition is assumed to decline slowly over time; this is modelled as increases of 0.125 in HAQ score occurring from time to time. HAQ scores are calculated so that a unit change in disability detected by this questionnaire is 0.125; a patient may have a minimum score of 0 and a maximum of 3.0 (see Appendix 1, page 87 for details of HAQ). All patients are followed through to death, which necessarily occurs while on some form of treatment (DMARD or palliation). Mortality risk is assumed to be dependent on current HAQ score, as well as age and sex.

4.4.1 Strategies compared using the BRAM

Table 12 shows the two strategies for using DMARDs considered in this report. These treatment pathways were based on a systematic review of the literature on treatment of RA patients with DMARDs and a survey of rheumatologists in the UK in 2002.[47]

The combination of methotrexate and ciclosporin was not used if either of its components had been quit on the grounds of toxicity. In each case, the comparison is made between the strategy as shown (with anakinra "in the middle") and without anakinra. Because of current supply problems with etanercept (personal communication Wyeth Medical Information 22/1/03), each strategy was subdivided according to the use or non-use of etanercept; versions using etanercept are referred to as strategies 1A and 2A; without etanercept, strategies 1B and 2B. Further comparisons were made moving anakinra to the end of the list, after combination therapy; again, the comparison in each case was between the strategy with anakinra last, and without anakinra. Thus a total of eight pair-wise comparisons could be made for any set of parameter values.

Table 12: Strategies used in the BRAM for assessment of anakinra

	Strategy 1	**Strategy 2**
Sequence of DMARDs used	sulfasalazine methotrexate (MTX) leflunomide (etanercept) infliximab **anakinra** gold (GST) azathioprine ciclosporin (CyA) combination MTX + CyA	sulfasalazine methotrexate (MTX) hydroxychloroquine gold (GST) leflunomide (etanercept) infliximab **anakinra** azathioprine ciclosporin (CyA) combination MTX + CyA

(Note that neither of these strategies uses penicillamine, because our survey revealed that this treatment was not widely used.)

4.4.2 Starting point for comparisons

Since both treatment arms in any comparison start with the same initial drug sequence, early costs and QALYs are the same. Therefore, in each case, the starting point for comparison was the point of divergence between the two options compared. All patients in the model were started at the beginning of the sequence; patients who did not reach the point of divergence were not included in the analysis. Costs and QALYs were accumulated only from the point of divergence, and discounted (at 6% and 1.5% respectively) to that point. In principle, it would be possible to start the model at the divergence point. This would, however, require knowledge of the distribution of patients by age, sex and HAQ score at the divergence point, and thus separate starting populations for each comparison. The method used requires only a single data set for its starting population.

The model assumes a constant risk of increase of HAQ score while on treatment and that an individual's HAQ score increases gradually and in steps of 0.125, apart from the effects of starting and ending treatment. While HAQ can change at any stage of disease, and is known to be more labile in early disease, the assumption of a gradual increase in HAQ is reasonable for the parts of the model where comparisons are being made, as the model applies to the later stages of the disease. The rate of increase of HAQ was chosen to reflect the empirically observed increase reported by Scott *et al*.[136]

Notice also that, for a particular strategy, the same total sequence of DMARDs is used in the non-anakinra branch whether anakinra appears in the middle or last. However, the point of divergence is different, and so the total costs and QALYs counted will also be different.

4.4.3 Data used in the BRAM for anakinra

What follows is a list of the data used in the BRAM for anakinra. Data for anakinra are essentially drawn from this review; other data have been taken from the literature.

Table 13 shows the initial age and sex distribution, based on Wiles *et al*.[8]

Table 13: Initial age and sex distribution

age	15 – 24	25 – 34	35 – 44	45 – 54	55 – 64	65 – 74	75 – 84	total
male	0.6	1.2	2.3	5.8	6.4	9.3	5.2	30.8
female	2.9	5.8	9.9	16.9	14.0	15.1	4.6	69.2

The starting distribution of HAQ scores is shown in Table 14, based on Wiles *et al*.[66] Note that although only three different values were used at the start, natural HAQ increases mean that a much greater variety applies at the point of divergence between branches in any strategy.

Table 14: Starting distribution of HAQ scores

HAQ	0.25	0.75	1.5
%age	25	50	25

Time spent on any DMARD is drawn from a Weibull distribution. A random variable X has a Weibull distribution with shape parameter a and scale parameter b if $\left(\frac{X}{b}\right)^a$ has an exponential distribution with unit mean. The Weibull distribution is more general than the constant-risk exponential distribution in that it reduces to the exponential distribution when $a = 1$. If $a < 1$, then the risk decreases over time, while if $a > 1$, the risk increases over time. Parameters a and b are shown in Table 15. For convenience, the mean of the distribution is also shown.

For anakinra, our review gave a withdrawal rate of 23 % at 24 weeks. With no data beyond this point, we fitted an exponential distribution to this one point, to be varied in sensitivity analysis. (Although we had some information about timing of withdrawals up to 24 weeks, this was not felt to be a sensible basis on which to extrapolate the shape of the curve.)

Table 15: Times to quitting DMARD

DMARD	*a*	*b* (yrs)	mean (yrs)	source
anakinra	1	1.77	1.77	see text
azathioprine	0.73	1.60	1.95	Hawley and Wolfe [137]
ciclosporin	0.79	7.62	8.71	Marra *et al* [138]
etanercept	0.73	12.34	15.03	Geborek *et al* [139]
gold	0.71	3.08	3.85	Maetzel *at al* [43]
hydroxychloroquine	1	3.62	3.62	Maetzel *at al* [43]
infliximab	0.73	5.96	7.26	Geborek *et al* [139]
leflunomide	0.66	1.7	2.28	Siva *et al* [140]
methotrexate	0.77	4.62	5.39	Maetzel *at al* [43]
penicillamine	0.62	1.86	2.69	Pincus *et al* [52]
sulfasalazine	0.71	2.76	3.45	Maetzel *at al* [43]
combination	1	1.74	1.74	Tugwell *et al*[141] Gerards *et al*[142]

(Penicillamine appears in this table as it has the lowest value of the shape parameter *a*; we used this value in the sensitivity analysis for anakinra.)

Toxicity of DMARDs was only an issue for methotrexate and ciclosporin because toxicity to either of these agents would mean that combination therapy with methotrexate and ciclosporin would not be included as a therapeutic option. For other DMARDs cessation because of toxicity or inefficacy has the same consequence in our model i.e. use of the DMARD next in sequence. For ciclosporin it was assumed drug cessation was due to toxicity with a probability of 0.8 regardless of time spent on drug.[143] For methotrexate, the probability p was set to depend on the time t years on the drug, by the formula $p = 0.362 + 0.115e^{-0.457t}$, which was derived from a comparison between the survival curves given in Maetzel *et al*.[43]

Costs are made up of drug costs plus monitoring costs. For all DMARDs, there are higher costs on starting than there are for continued use. The total cost for time on any treatment is modelled as a one-off starting cost followed by a steady annual usage cost. The only ones that are relevant for the comparisons in this report are for treatments that come after the point of divergence. For completeness, all costs are shown. The price year is 2002 in each case. The unit costs of the various inputs are shown in Table 16 and Table 17. The monitoring assumptions are listed in Table 18.

Table 16: Unit costs for tests and visits

Test		**Source**
Full Blood Count	3.77	Newchurch Ltd., National Pathology Alliance Benchmarking Report: Haematology and Blood Transfusion 2000/2001. London: Newchurch. 2002
ESR	2.91	
Biochemical Profile	3.63	
Chest X-ray	14.75	Newchurch Ltd., Radiology Benchmarking Report: 1999/2000. London: Newchurch. 2001
Urinalysis	0.08	Newchurch Ltd., National Pathology Alliance Benchmarking Report: Haematology and Blood Transfusion 2000/2001. London: Newchurch. 2002
Visits		
GP	18.00	PSSRU[144]
Hospital OP	86.00	
Hospital IP (per day)	191.00	
Specialist nurse visit	43.00	assumed half of OP visit

Table 17: Unit costs for drugs (sources: Drug tariff / Mims, Dec 2002)

Treatment	Cost	Assumptions
anakinra	£20.47 per day	100 mg/day
azathioprine	3×15.2p per day	150mg per day
ciclosporin	£5.187 per day	70kg patient; 3.25mg/kg per day
etanercept	£89.38 per dose	102 doses per year
gold	£9.36 per month	50 mg amp, administered at GP visit
hydroxychloroquine	11.4p per day	300mg per day
infliximab	£451.20 per vial	70kg patient, drug wastage if full vials not used, cost per administration £124
leflunomide	£1.55 per day	20mg per day
methotrexate	11.4p per 2.5mg tablet	15mg per week
sulfasalazine	37.5p per day	2.5g per day

Table 18: Monitoring assumptions

Treatment	Pre-treatment	On treatment
palliation		OP visit every 3 months
anakinra	FBC, ESR, BCP, 4 specialist nurse visits	FBC, ESR, BCP monthly at specialist nurse visit, GP visit every 3 months
azathioprine	FBC, ESR, BCP	FBC and BCP weekly for 6 weeks, then every 2 weeks for 3 visits, then monthly
ciclosporin	FBC, 2×BCP, ESR, urinalysis	FBC, BCP every 2 weeks for 4 months, then BCP monthly
etanercept	FBC, ESR, BCP, CXR	FBC, ESR, BCP at weeks 2, 4, 8, 12, then every 3 months
gold	FBC, ESR, BCP, urinalysis	FBC, BCP, urinalysis every week for up to 21 injections, then every 2 weeks for 3 months, then every 3 weeks for 3 months, then monthly. Treatment given by i.m. injections
hydroxychloroquine	FBC, ESR, BCP	FBC, ESR, BCP every 3 months
infliximab	FBC, ESR, BCP, CXR	FBC, ESR, BCP at weeks 2, 6 and every 8 weeks (at time of infusions)
leflunomide	FBC, ESR, BCP, urinalysis	FBC every 2 weeks for 6 months, every 8 weeks thereafter. BCP monthly for 6 months, every 8 weeks thereafter
methotrexate	FBC, ESR, BCP, CXR	FBC, BCP every 2 weeks for 4 months then monthly
sulfasalazine	FBC, ESR, BCP	FBC every 2 weeks and BCP every 4 weeks for 12 weeks, then FBC and BCP every 3 months

(FBC = full blood count, ESR = erythrocyte sedimentation rate, BCP = biochemical profile, CXR = chest X-ray)

Combining the above information leads to the model inputs shown in Table 19. It should be noted that palliation does not include hospitalisation, although this may be higher for RA patients with no DMARD options, as we could not quantify this.

Table 19: Treatment costs

Treatment	Start-up (£)	Annual usage (£)
palliation	0	344
anakinra	182.31	8080.32
azathioprine	656.71	1286.78
ciclosporin	331.22	2963.63
etanercept	473.61	9513.64
gold	2538.55	1450.08
hydroxychloroquine	96.31	426.74
infliximab	1758.51	9867.24
leflunomide	933.81	1124.60
methotrexate	484.66	1156.37
sulfasalazine	552.42	510.10
combination	331.22	2999.20

Basic mortality comes from standard life tables. A relative risk of 1.33 per unit HAQ is applied.[145]

In the base case, it is assumed that there is a mean time of 4 years between each 0.125 unit increase in HAQ. This reflects a mean decline (increase) of 0.031/yr.[136] Table 20 shows the improvement (reduction) in HAQ for starting each DMARD. If the patient's HAQ score at the time of starting a DMARD is less than the reduction given, then the HAQ score reduces to zero. The reduction actually applied is used for the increase in HAQ score on quitting the DMARD, except that HAQ cannot go above 3. For example, a patient starting methotrexate with a HAQ score of 0.25 would improve to a HAQ of 0. If the same patient has a HAQ score of 0.125 when quitting methotrexate, the HAQ score increases to 0.375.

Table 20: Improvement in HAQ for starting each DMARD

DMARD	HAQ reduction	Sources
anakinra	0.25	From this review
azathioprine	0.25	Assumed to be at the lower end of effectiveness as there is no reliable data on which to base estimates
ciclosporin	0.375	Zeidler HK *et al* [146]
etanercept	0.5	Jobanputra P *et al*.[39] Based on meta-analysis of available trials.
gold	0.375	Munro R *et al* [41]
hydroxychloroquine	0.25	HERA study group [147]
infliximab	0.5	Jobanputra P *et al*.[39] Based on meta-analysis of available trials.
leflunomide	0.375	Scott and Strand [136]
methotrexate	0.5	Wyeth Laboratories [148]
sulfasalazine	0.375	Scott and Strand [136]
combination	0.25	As for azathioprine

Conversion from HAQ to QALYs is by the formula $QoL = 0.862 - 0.327HAQ$ calculated from the data set supplied by Nigel Hurst, and reported in Hurst *et al*.[149] We have assumed that start and end effects can be modelled as one-off deductions equal to 0.2 years times the change in QoL score.

4.4.4 Results

Results from the model are in the form of comparisons between two options, one containing anakinra ("with Ana") and one not ("no Ana"). In each case, the mean cost and QALYs per patient are given. These are calculated from the point of divergence between the options, and discounted to that point at 6% per annum for costs and 1.5% for QALYs, in accordance with Treasury guidelines. The results are subject to statistical error from the sampling used in the model. Quasi-standard errors (Q.S.E.) are quoted for costs and QALYs. These reflect the sample sizes used and are given simply to show that an adequate number of replications of the model was made. For each option, the %age of (virtual) patients ending on palliation has been quoted. This shows what proportion of patients completed a sequence of DMARDs. The results from the two branches must be treated as unpaired data, so the square of the quasi-standard error of the difference is the sum of the squares of the individual quasi-standard errors. ICERs are quoted as the ratio of mean differences, followed by an approximately 95 % quasi-confidence interval obtained using the formula on page 91 of Armitage and Berry[150] to the reciprocal of the ICER.

Unless otherwise stated, the results with anakinra "in the middle" are based on 1,000,000 patients reaching the divergence point. For anakinra last, a much smaller proportion of the original population reaches the divergence point, increasing the running time for the model if the number of patients is fixed. However, the variation among patients is reduced considerably, so a sample of 100,000 proved adequate. In some cases, the run-length was increased in order to reduce the size of the quasi-confidence intervals; such cases are noted in the results tables.

Strategies 1 and 2 are as defined in Table 12, page 72. Strategies 1A and 2A include etanercept; strategies 1B and 2B do not. The effect of removing etanercept is that patients reach the divergence point earlier, and therefore tend to be younger. Since all patients are followed through to death, the total costs and QALYs are therefore higher than for the corresponding strategy with etanercept. Similarly, although the patient pathways in the "no anakinra" options in each strategy are the same whether anakinra is in the middle or last, the point from which costs and QALYs are counted is different, and the criterion for reaching the point of divergence is also different.

4.4.4.1 Base Case Results

The base-case costs, QALYs and ICERs for anakinra used in either treatment strategy, with and without the availability of etanercept are shown in Table 21, below. For fuller details please refer to Appendix 8, page 97.

Table 21: Base-Case ICER Calculations

Base-Case ICER Calculations									
			Difference in cost per patient (£)		QALYs per patient		ICER (£/QALY)		
Place in DMARD sequence	DMARD sequence	Is etanercept available?	mean	q.s.e.	mean	q.s.e.	ICER	low	high
Middle	1	Yes	9477	7.8	0.016	0.0030	604 000	436 000	985 000
		No	9647	11.1	0.025	0.0046	379 000	278 000	597 000
	2 (early HCQ and gold)	Yes	9639	16.0	0.025	0.0054	385 000	270 000	674 000
		No	9843	16.3	0.035	0.0059	278 000	209 000	415 000
Last	1	Yes	11508	24.3	0.088	0.0106	131 000	106 000	173 000
		No	11682	17.3	0.111	0.0082	105 000	92 000	124 000
	2 (early HCQ and gold)	Yes	11441	24.1	0.105	0.0100	109 000	91 000	134 000
		No	11551	24.3	0.109	0.0110	106 000	88 000	132 000

q.s.e. = quasi standard error of the difference in means. This reflects only the uncertainty due to sampling within the model, not the parameter uncertainty. It can be reduced by increasing the number of virtual patients in the model and is quoted to show that a sufficient number have been used.
QALY = quality adjusted life-year
ICER = incremental cost-effectiveness ratio
low/high = low and high ends of ~95% quasi-confidence intervals (reflecting only sampling uncertainty within the model)

4.4.5 Sensitivity Analysis

As the best base-case ICER estimate was over £100K/QALY, i.e. above that which is generally accepted as "value for money" within the current NHS budget envelope, we undertook sensitivity analyses only in the direction that would favour anakinra. The effect of the following assumptions was explored: time on anakinra; start and end effects; effectiveness of anakinra. A best-case scenario for anakinra was produced combining these. The effect on the ICER is summarised in Table 22, page 80. Please see Appendix 9, page 99 for full details of the simulations for the sensitivity analyses.

Time on anakinra
As noted above, the time on anakinra was based on a single time-point in the base case. As an alternative to the exponential distribution, we tried the lowest value (0.62) of the shape parameter *a* for any of the DMARDs in Table 15, page 74. (This is the most favourable to anakinra.) To fit 23% withdrawal at 24 weeks requires $b = 4.02$. The mean of the new distribution is 5.80 years, compared to 1.77 years in the base case.

Start and end effects
For the sensitivity analysis the one-off loss of QALYs at start and end of DMARDs were omitted.

Effectiveness of anakinra
To see the effect of benefit of anakinra on HAQ scores, we changed the HAQ improvement due to anakinra from 0.25 to 0.5. It must be emphasised that there is no evidence to support this value: this is purely a "what if" analysis.

Best case scenario
We combined the estimates of the three parameters above used in the sensitivity analyses to produce the best case scenario.

Table 22: ICER Calculations for Sensitivity Analyses

ICER Calculations for Sensitivity Analyses						
				ICER (£/QALY)		
Parameter varied	**Place in DMARD sequence**	**DMARD sequence**	**Is etanercept available?**	**ICER**	**low**	**high**
Time on anakinra (mean 5.8 years instead of 1.77)	**Middle**	**1**	**Yes**	301 000	250 000	377 000
			No	245 000	209 000	295 000
		2	**Yes**	198 000	177 000	225 000
			No	174 000	157 000	195 000
	Last	**1**	**Yes**	83 000	74 000	94 000
			No	85 000	76 000	98 000
		2	**Yes**	89 000	79 000	101 000
			No	81 000	72 000	91 000
Start and end effects (there is no loss of QALYs at start and end of DMARDs)	**Middle**	**1**	**Yes**	277 000	205 000	431 000
			No	199 000	156 000	272 000
		2	**Yes**	201 000	164 000	258 000
			No	166 000	138 000	206 000
	Last	**1**	**Yes**	97 000	82 000	118 000
			No	88 000	75 000	107 000
		2	**Yes**	84 000	73 000	99 000
			No	82 000	71 000	98 000
Effectiveness of anakinra (arbitrary assumption that effect of anakinra on HAQ score is equal to best of other DMARDs i.e. 0.5)	**Middle**	**1**	**Yes**	77 000	70 000	88 000
			No	72 000	66 000	80 000
		2	**Yes**	72 000	67 000	78 000
			No	68 000	63 000	74 000
	Last	**1**	**Yes**	59 000	53 000	66 000
			No	62 000	53 000	75 000
		2	**Yes**	54 000	50 000	60 000
			No	57 000	53 000	61 000
Best-case scenario (Combining the above three parameter changes)	**Middle**	**1**	**Yes**	50 000	48 000	51 000
			No	48 000	47 000	50 000
		2	**Yes**	46 000	44 000	47 000
			No	45 000	43 000	46 000
	Last	**1**	**Yes**	38 000	36 000	40 000
			No	38 000	36 000	41 000
		2	**Yes**	38 000	36 000	41 000
			No	37 000	35 000	39 000

q.s.e. = quasi standard error of the difference in means. This reflects only the uncertainty due to sampling within the model, not the parameter uncertainty. It can be reduced by increasing the number of virtual patients in the model and is quoted to show that a sufficient number have been used. ***QALY*** = quality adjusted life-year ***ICER*** = incremental cost-effectiveness ratio. ***low/high*** = low and high ends of ~95% quasi-confidence intervals (i.e. sampling uncertainty within the model)

5 IMPLICATIONS FOR OTHER PARTIES

The substantial economic impact of rheumatoid arthritis in terms of direct and indirect costs has been highlighted elsewhere in this report. Studies indicate a great range of potential costs that cannot readily be explained by socio-economic or clinical factors. However it is apparent that a minority of patients may account for a great proportion of the direct medical costs. Costs incurred by individuals, in a cohort of early arthritis patients, are similar to costs incurred by health care services. Costs incurred by family and friends in terms of forgone paid work, forgone leisure time and other factors greatly exceed costs incurred by individuals and health care services. Clearly this could have an impact on the quality of life of patients and carers. Further, physical disability resulting in difficulties in self-care, and work disability has implications for personal social services.

6 FACTORS RELEVANT TO NHS

Use of anakinra can be anticipated to place a demand on out-patient rheumatology facilities, with particular implications for out-patient nurse workload. These professionals are likely to take the lead in teaching patients and carers to self-administer injections, provide back-up support and disease and drug monitoring services. The availability of such specialist nurses in rheumatology varies across the NHS.

There are currently no data on which to base an assessment of the potential impact of anakinra on joint damage in patients with RA. If a reduction in joint damage is apparent this has the potential to reduce the need for surgery in patients with RA. This may in turn lead to a reduced demand for orthopaedic services.

On the basis of the evidence available the most difficult issue for professionals is likely to be identifying the true place in therapy of anakinra amongst other treatments for RA.

7 DISCUSSION

7.1 Main clinical effectiveness results

Anakinra, at the higher doses evaluated, demonstrated modest efficacy compared to control, in terms of improving symptoms of RA, when used as both monotherapy and in combination with methotrexate. The effect seen was relatively consistent across the trials with a RR with the 'licensed dose' of anakinra of achieving an ACR 20 of 1.6, ACR 50 2.3, ACR 70 3.1 with respective NNTs of 7, 11 and 33, based on the public domain data. A response was generally evident early (within 4 weeks) with no waning of treatment effect evident over the medium term

Three of the trials evaluated ranges of doses of anakinra. Whilst a clear dose response was not evident across all the dose ranging studies there was a suggestion of increased response with increasing dose. Optimal efficacy was seen at the higher doses that are in line with the licensed dose of 100mg daily. No evidence of efficacy was apparent with the low doses of anakinra (≤ 30mg/day) studied in trial 0182.

For the composite endpoint ACR response benefit with anakinra was slightly greater when used in combination with methotrexate than when used as monotherapy. This may reflect differences in study designs and populations and perhaps late response to continued methotrexate. No subset of patients were identified who had greater or lesser likelihood of response to anakinra.

ACR endpoint data for study 0757 a large pragmatic safety study have not been made available. This is of concern, due to the size and 'real life' design of this trial. We consider that this study and the ACR endpoint data collected are absolutely valid in informing clinical practice. Pragmatic trials that reflect average clinical practice tend to have more external validity than those conducted on highly selected patient populations. We do not believe that because the primary purpose of this trial was to look at safety that it is *"inappropriate and misleading to draw any conclusions from any efficacy assessments taken from this study"*? The key issue is whether the study design used (in this case a randomised, double-blinded placebo-controlled trial with before and after measurements of effectiveness outcomes) is an appropriate design from which to be able to draw valid conclusions about effectiveness. It clearly is.

Although a trial undertaken in an every day clinical setting will have more heterogeneity among the participants than a trial undertaken on a highly selected population with restrictive inclusion criteria, this does not necessarily mean that the results will be confounded. One of the benefits of the randomised design is that, not only does it reduce selection bias, but it minimises or avoids the effects of both known and unknown confounders by ensuring that the groups compared have a similar distribution of baseline characteristics. In this trial the patient characteristics of disease duration, concomitant medications and co-morbid conditions, that the company allude to as potential confounders, are randomly distributed between the arms, reducing the risk that they will confound the analysis. Moreover the large size of this trial helps to minimise the risk of this happening by chance. Indeed the reported baseline characteristics of the two groups in this trial confirm that there were no significant imbalances in NSAID, corticosteroid, methotrexate, or other DMARD use between the anakinra and placebo participants, nor in baseline demographic characteristics or disease status (Tables 8-7 and 8-8 of the trial report). In the light of this an analysis of differences in clinical outcomes is methodologically sound and valid.

Because about half the relevant data on effectiveness has been withheld and this is the data, which most reflects the average RA clinic population, it is difficult to make an accurate estimate of likely effectiveness of anakinra in actual clinical practice. It is probable that the data that has been released into the public domain overestimates the effectiveness that would be seen in a clinic context. In the absence of data we made an educated estimate about the effectiveness of anakinra seen in trial 0757 (described earlier). The derived estimate combined with data from earlier trials, using a random effects model, gives our best summary estimate of effectiveness for the ACR 20 response; RR 1.43 (95% CI 1.16 to 1.76), RD 0.11 (95% CI 0.04 to 0.18), NNT 9 (95% CI 6 to 25).

No conclusion can be made on effect on disease progression given current data. Study 0560 (monotherapy) suggested that treatment may be associated with a slowing of disease progression as measured by the Larsen score. This endpoint was not presented for the other studies. Trial 0145 evaluated disease progression using the modified Sharp score. This trial is now complete but full data are not yet available. We have serious reservations about post-hoc analyses that claim benefits in clinical non-responders especially because of the problems of

measurement error with radiographic outcomes. Rheumatologists may feel justified in employing therapeutic agents in essence for prophylactic purposes where patients experience no immediate benefits. However whether patients find this approach acceptable allowing for ISRs and other hazards of IL-1Ra would need to be determined. In addition since other DMARDs also inhibit radiographic damage and have the potential for improving clinical outcomes for patients who have not previously used them it would seem appropriate for Rheumatologists to use untested DMARDs rather than continue with anakinra in the face of continued disease activity.[151]

Anakinra has not been compared head to head with other DMARDs. Such trials are required to inform clinical practice in order to place this drug amongst other DMARDs for the treatment of RA. In the absence of head to head trials an adjusted indirect comparison of NNTs for ACR suggests that anakinra is less effective than other biologic and other DMARDs. This could be due to different trial conditions or populations or represent a true treatment difference.

Injection site reactions were common with anakinra treatment but were generally mild or moderate and transient. Less than 10% of patients withdrew from treatment due to ISRs. These reactions may however have lead to unblinding of treatment. Only study 0145 used adjusted methodology to protect against this. Unblinding due to ISRs has the ability to influence the perceived response for subjective markers (e.g. SJC, ACR response). However objective endpoints (e.g. ESR, CRP) should be less subject to unblinding. Benefits with anakinra at therapeutic doses were demonstrated in both subjective and objective endpoints across the clinical trials.

Serious adverse events were uncommon and included serious infections and neutropenia. To date an increase in opportunistic infections such as TB has not been reported. Increased incidence of malignancy was not evident but data and exposure are still limited. The BSR biologics register is monitoring adverse events over the longer term.

7.2 Economic evaluation

There are no relevant economic evaluations in the published literature. The economic model included in the Amgen submission to NICE contains structural flaws that make its estimate of the cost-utility of anakinra unreliable.

Results of the Birmingham Rheumatoid Arthritis Model:

- The BRAM gives a base-case estimate of the ICER of anakinra of between £106,000/QALY to £604,000/QALY.
- This model uses data from public domain trial results only. These recruited a highly selective patient population and may well overestimate the cost-effectiveness that anakinra would achieve in an average clinic population.
- Used as a last resort treatment it has a more favourable ICER than when used earlier in the treatment pathway. This is because anakinra displaces cheaper drugs.
- In the current situation, where supplies of etanercept are limited, the ICER appears to be slightly more favourable than it would be were etanercept readily available.
- Although the ICER is slightly more favourable when used in drug sequence 2 (with early hydroxychloroquine and gold) the choice of this drug sequence is usually determined by the patient characteristics and disease presentation.[47]
- In the sensitivity analyses quite substantial variations were made in key parameters and ICERs were shown to be responsive.
- ICERs did not drop below £50,000/QALY in any univariate analysis

- The best-case scenario produced ICERs between £37k and £50k/QALY. These figures, however, are highly improbable and are based on the generous assumption that doubles anakinra's estimated effectiveness, for which there is no empirical evidence.

Assuming that anakinra is used as a last resort DMARD, the Amgen model estimate of £16,545/QALY is lower than our very best case scenario and appears to be unsustainable. This is due to multiple inappropriate structural assumptions and errors of the Amgen model.

The BRAM produces an ICER for anakinra substantially higher than those for infliximab and etanercept. This finding is consistent with the indirect comparison of effectiveness for ACR responses (a parameter not used in the model) which suggest that anakinra has a substantially higher NNT. However, it must be borne in mind that patients may respond to anakinra when they have not responded to other biologics, like the TNF inhibitors, as they have a different mechanism of action. Thus anakinra may produce a clinically significant and important improvement in some patients that they could not otherwise have achieved.

7.3 Assumptions, limitations and uncertainties

A key strength of this review was the expert input received at all stages that ensured a clinically relevant perspective was maintained throughout. Sensitive searches were conducted to maximise retrieval of relevant data.

Included studies were of high quality as judged by the Jadad scale. Withdrawal from treatment was handled variously using last observation carried forward or non-responder imputation. It is not known if these method of analyses could have introduced unforeseen biases. However the FDA and EMEA evaluated the robustness of this approach with sensitivity analyses assuming a worst case scenario. Other than for study 0560 this did not alter the conclusions of the trials in relation to ACR response.

The double-blind trials conducted can be considered of short duration (up to 6 months with the exception of 0145) for a chronic disease such as RA. Longer term open label follow up studies are however available. Evaluation of the studies is complicated by the use of a wide range of doses, both fixed dose and doses by body weight, across the clinical trial programme.

Approximately 75% patients completed the trials. Reasons for withdrawal varied across the treatment and control groups. Generally adverse events were a more frequent reason for withdrawal with the higher doses of anakinra evaluated, and lack of efficacy with control.

There is the potential for bias due to unblinding due to adverse events most notably ISRs. Only one study used additional methods to protect against this.

Efficacy data were not available for the large pragmatic trial 0757. This is a major weakness in evaluating the effectiveness of anakinra in patients with RA. Given the size of this trial its findings are likely to overshadow those seen in the smaller studies. (See earlier comments.) In the absence of the published results of this trial we made an educated guess on the trials likely findings. Whilst this analysis should be interpreted with caution it provides a sensitivity analysis around the primary outcome of ACR 20 response. Additionally full data on the disease progression endpoints for study 0145 were not available.

No direct comparisons of anakinra with DMARDs or anti-TNFs are available. These are required to inform clinical practice. In the absence of this an adjusted indirect comparison was undertaken to help inform practice, this should be interpreted with caution and the findings tested in direct head to head trials.

An assessment of dose response across all endpoints using individual patient data is required to identify whether a true dose response exists in studies 0560 and 0180. Sensitivity analysis assuming no dose response did not alter our findings in relation to ACR response.

Anakinra is too new to be able to know about any effect, if any, it may have on the need for joint replacement. Therefore joint replacement effects have not been modelled.

Although mortality benefits have been included in the model, these have been assumed to relate solely to HAQ scores.

There is very limited evidence, if any, reliably relating ACR responses to quality of life. Consequently the BRAM uses HAQ score changes as a predictor of QALY scores. However all studies, including those for the comparator drugs, have limited data on HAQ scores. Therefore the model is based on crude estimates of the effect on HAQ of all treatments.

Trial data is only available to 24 weeks, therefore continued benefit has been derived by extrapolation. There is a very wide range of time on anakinra consistent with the current data, consequently there is a large degree of uncertainty in the results.

The economic evaluation takes an NHS perspective and may therefore underestimate the true cost-effectiveness of anakinra as a considerable proportion of the cost of uncontrolled disease falls on patients and carers.

7.4 Need for further research

A number of other therapeutic approaches in RA are currently being investigated, these are summarise in Appendix 10, page 104.

For research that has already been conducted with anakinra research needs are

- the publication of the efficacy data from the large pragmatic study (0757) to enable the benefit of treatment to be fully evaluated
- publication of the 1 year radiology outcome data from study 0180 to evaluate the potential effects of treatment on disease progression. It is also important to identify whether any benefits on radiological measures are limited to patients who demonstrate a symptomatic response.

Current clinical trials with anakinra are of limited duration. RCTs are required to evaluate the efficacy, safety and cost of anakinra over the longer term in patients with such a chronic disease.

Comparative trials of anakinra with other DMARDs and biologic modifiers are needed to identify the comparative efficacy of these drugs and to guide clinical practice to optimise patient care. Additionally trials are required to assess the role of anakinra in the treatment of patients who have failed to achieve a benefit whilst taking infliximab or etanercept.

Studies with IL-1Ra given by continuous infusion to rats with collagen induced arthritis produced dramatic effects on soft tissue swelling and disease progression. Blood levels achieved in clinical trials with once daily s.c. dosing in humans with RA were much lower than those seen in the animal models. It is not known whether daily s.c. administration is sufficient to achieve continuous saturation of IL-1 receptors. A clinical trial in which IL-1Ra is delivered by continuous infusion or a slow release delivery system would address whether this apparent difference between species is related to sub-optimal dosing in humans. [26;152]

Suggestions that newer biologic therapies reduce radiographic damage without necessarily improving clinical outcomes need to be confirmed if treatments in the absence of a clinical response are to be justified.

Further research is required to assess the impact of DMARDs on joint replacement, mortality and quality of life.

As the pathogenesis of RA is complex, it may not be fully suppressed by monotherapy by blocking a single mediator. Optimal treatment in the future may require combinations of therapeutic agents that inhibit more than one mediator in a complex pathogenic network. [25] Controlled clinical trials are required in this area to inform clinical practice, before any such approaches are widely adopted.

Further research is needed to improve the utility of radiographic outcomes in clinical trials of RA either by building on existing efforts with plain radiographs or through the use of newer imaging methods.

8 CONCLUSIONS

Anakinra offers a new therapeutic approach for the management of RA. The clinical trials establish efficacy of anakinra in reducing the signs and symptoms of RA, most notably at the higher doses studied. Although modest efficacy is established the degree of clinical effectiveness is difficult to gauge because of the absence of data from a large pragmatic safety study. There are no studies of a direct comparison with other DMARDs or anti-TNF therapies. An adjusted indirect comparison suggests that anakinra may be significantly less effective at relieving the clinical signs and symptoms of RA, as measured by the ACR response criteria, than TNF inhibitors all used in combination with methotrexate. Such indirect comparisons should be interpreted with caution and assume generalisability of study results. Whilst safety over the short-term is established duration of exposure is still limited. Safety over the longer term is not yet known.

The independent economic model developed to evaluate the cost-effectiveness of anakinra in clinical practice gives a base-case estimate of the ICER for anakinra of between £106,000/QALY to £604,000/QALY. This ICER is substantially higher than those for infliximab and etanercept. However, patients may respond to anakinra when they have not responded to other biologics, as these agents have a different mechanism of action. Thus anakinra may produce a clinically significant and important improvement in some patients that they could not otherwise have achieved.

Appendix 1: Health Assessment Questionnaire[153]

Patient Label				Date:
We are interested in learning how your illness affects your ability to function in daily life. Please feel free to add any comments at the end of this form.				
PLEASE TICK THE ONE RESPONSE WHICH BEST DESCRIBES YOUR USUAL ABILITIES OVER THE PAST WEEK				
	Without ANY difficulty	With SOME difficulty	With MUCH difficulty	Unable to do
	Score = 0	Score = 1	Score = 2	Score = 3
1. DRESSING & GROOMING – Are you able to:	2.	3.	4.	5.
-Dress yourself including tying shoelaces and doing buttons?				
-Shampoo your hair				
2. RISING - ARE YOU ABLE TO:	3.	4.	5.	6.
-Stand up from an armless straight chair?				
-Get in and out of bed?				
3. EATING - ARE YOU ABLE TO:				
-Cut your meat?				
-Lift a cup or glass to your mouth?				
-Open a new carton of milk?				
4. WALKING - ARE YOU ABLE TO:				
-Walk outdoors on flat ground?				
-Climb up five steps?				

PLEASE TICK ANY AIDS OR DEVICES THAT YOU USUALLY USE FOR ANY OF THESE ACTIVITIES			
Cane		Devices used for dressing (button hook, zipper pull, long handled shoe horn, etc.)	
Walking frame		Built-up or special utensils	
Crutches		Special or built-up chair	
Wheelchair		Other (specify)	

PLEASE TICK ANY CATEGORIES FOR WHICH YOU USUALLY NEED HELP FROM ANOTHER PERSON			
Dressing and Grooming		Eating	
Rising		Walking	

Health Assessment Questionnaire - continued

	Without ANY difficulty	With SOME difficulty	With MUCH difficulty	Unable to do
	Score = 0	Score = 1	Score = 2	Score = 3
5. HYGIENE – ARE YOU ABLE TO				
-Wash and dry your entire body?				
-Take a bath?				
-Get on and off the toilet?				
6. REACH – ARE YOU ABLE TO				
-Reach and get a 5lb object (e.g. a bag of potatoes) from above your head)?				
-Bend down to pick up clothing from the floor?				
7. GRIP – ARE YOU ABLE TO				
-Open car doors?				
-Open jars which have been previously opened?				
-Turn taps on and off?				
8. ACTIVITIES – ARE YOU ABLE TO				
Run errands and shop?				
Get in and out of a car?				
Do chores such as vacuuming, housework or light gardening?				

PLEASE TICK ANY AIDS OR DEVICES THAT YOU USUALLY USE FOR ANY OF THESE ACTIVITES:			
Raised toilet seat		Jar opener (for jars previously opened)	
Bath seat		Long handled appliances for reach	
Bath rail		Other (specify)	

PLEASE TICK ANY CATEGORIES FOR WHICH YOU USUALLY NEED HELP FROM ANOTHER PERSON			
Hygiene		Gripping and opening things	
Reach		Errands and housework	

Scoring of HAQ

Add the maximum score for each of the 8 sections and divide by 8 to give a score between 0 to 3. If aid / device or help is needed the score for that activity automatically = 2 (unless 3 has already been ticked). Normal function = 0, Most severely affected = 3.

Appendix 2 : Assessment of response to DMARDs

American College of Rheumatology Response Criteria.[59]
Tender joint count
Swollen joint count
At least 3 of:

- global disease activity assessed by observer
- global disease activity assessed by patient
- patient assessment of pain
- physical disability score (e.g. HAQ)
- acute phase response (e.g. ESR or CRP)

Response is defined as ACR20, ACR50 or ACR70 where figures refer to %age improvement of the clinical measures shown above.

European League Against Rheumatism (EULAR) response criteria.[154;155]

This measure is referred to as the DAS (disease activity score). Currently the DAS28 based on a simplified method is favoured for use. The DAS28 is calculated from the following formula:
DAS28 =

(0.555 x square root of tender joint count using 28 defined joints)
+ (0.284 x square root of swollen joint count using 28 defined joints)
+ (0.7 ln (ESR))
+ (0.0142 x patient global assessment of disease activity on 0-10 visual analogue scale).

Paulus response criteria[156]

Responses in 4 of 6 selected measures are required for improvement. Improvement by 20% or more in the following measures is required (the threshold for % improvement may be increased, e.g. to 50%, 70% as for ACR responses):

- Early morning stiffness
- ESR
- Joint pain or tenderness score
- Joint swelling score
- Patient overall assessment of current disease severity improved by $\geq$2 grades on 5-point scale, or from grade 2 to 1.
- Physician overall assessment of current disease severity improved by $\geq$2 grades on 5-point scale, or from grade 2 to 1.

Appendix 3 : Notes on radiographic scoring methods

Modified Sharp Method[157]

Radiographs of hands, wrists and feet are scored. 46 joints are scored for erosions. Erosions are scored on a 6-point scale. A score of 0 indicates no new erosion and no worsening of an existing erosion. Each point increase indicates occurrence of a new erosion or 20% worsening of an existing erosion. 42 joints are scored for narrowing on a 5-point scale. A score of 0 indicates no narrowing, 1 indicates minimal narrowing, 2 loss of 50% of the joint space, 3 loss of 75% of the joint space and 4 complete loss of the joint space. Scores for joint space narrowing and erosions are summed to give a total Sharp score.

Larsen scoring method

Radiographs of the hands and wrists are scored. Fifteen areas are examined. Dislocation and bony ankylosis are considered; if they are present, the scoring is based on the concomitant bone destruction. Maximum score (total for both hands) is 150.[158]

0 =	normal
1 =	slight abnormality, including 1 or more of the following lesions: periarticular soft tissue swelling, periarticular osteoporosis, and slight joint space narrowing
2 =	definite early abnormality, including definite erosion, with or without joint space narrowing
3 =	medium destructive abnormality
4 =	severe destructive abnormality
5 =	mutilating abnormality (the original articular surfaces have disappeared)

Appendix 4: American College of Rheumatology revised criteria for classification of functional status in rheumatoid arthritis[159]

Class	1 DESCRIPTION
Class I	Completely able to perform usual activities of daily living (self-care, vocational, and avocational)
Class II	Able to perform usual self-care and vocational activities, but limited in avocational activities
Class III	Able to perform usual self-care activities, but limited in vocational and avocational activities
Class IV	Limited ability to perform usual self-care, vocational, and avocational activities
Usual self-care activities include dressing, feeding, bathing, grooming, and toileting. Avocational (recreational and/or leisure) and vocational (work, school, homemaking) activities are patient-desired and age and sex-specific.	

Appendix 5: Yield from Medline and Embase Searches

Date: 10 Dec-2002
Database: Medline <1966 to present>

Set	Search	Results
1	exp Arthritis, Rheumatoid/	64573
2	exp Receptors, Interleukin-1/ or receptors interleukin 1.mp.	2357
3	(IL-1RA or IL 1RA).mp.	1768
4	anakinra.mp..	17
5	kineret.mp.	3
6	SIALOGLYCOPROTEINS/	5095
7	Recombinant Proteins/	92451
8	or/2-7	99041
9	1 and 8	494
10	randomized controlled trial.pt.	169545
11	controlled clinical trial.pt.	62509
12	randomized controlled trials/	26378
13	random allocation/	46502
14	double blind method/	71756
15	single blind method/	6954
16	or/10-15	286786
17	(animal not human).sh	2624439
18	16 not 17	273317
19	clinical trial.pt.	345108
20	exp clinical trials/	138904
21	(clin$ adj15 trial$).ti,ab.	86668
22	(singl$ or doubl$ or trebl$) adj25 (blind$ or mask$).ti,ab.	70784
23	Placebos/	21852
24	placebo$.ti,ab.	75840
25	random$.ti,ab.	251875
26	research design/	40192
27	or/19-26	605915
28	27 not 17	563903
29	28 not 18	301805
30	29 or 18	575122
31	9 and 30	95
32	from 31 keep 1-95	95

Date: 10-Dec 2002
Database: EMBASE <1988 to present>

Set	Search	Results
1	exp Rheumatoid Arthritis/	38527
2	Interleukin 1 Receptor Blocking Agent/ or Interleukin 1 receptor antagonist.mp.	3022

3	exp Interleukin 1/ or interleukin 1.mp.	21123
4	(IL-1RA or IL 1RA).mp.	1619
5	exp Recombinant Interleukin 1 receptor blocking agent/	196
6	anakinra.mp.	35
7	kineret.mp.	21
8	or/2-7	22483
9	1 and 8	1129
10	limit 9 to human	990
11	randomized controlled trial/	67095
12	exp clinical trial/	246318
13	exp controlled study/	1425624
14	double blind procedure/	44637
15	randomization/	4695
16	placebo/	58995
17	single blind procedure/	3771
18	((control$ adj (trial$ or stud$ or evaluation$ or experiment$).mp.	85364
19	((singl$ or doubl$ or trebl$ or tripl$) adj5 (blind$ or mask$)).mp.	64321
20	placebo$ or matched communities or matched schools or matched populations).mp.	97807
21	(comparison group$ or control group$).mp.	93788
22	(clinical trial$ or random$).mp.	417278
23	(quasiexperimental or quasi experimental or pseudo experimental).mp.	813
24	matched pairs.mp.	1325
25	or/11-24	1734786
26	10 and 25	478
27	from 26 keep 1-478	478

Appendix 6: List of included and excluded studies for effectiveness review.

Citation		Inclusion?	Publication type and reason for exclusion / comment
1	Cohen et al 2002[160]	Yes	Abstract. Trial 0180 HAQ scores at numerous time points
2	Bresnihan, McCabe et al 2001[161]	Yes	Abstract. Trial 0560. Modified Sharp score
3	Bresnihan, Chan et al 2001[162]	Yes	Abstract. Trial 0560. Productivity
4	Emery et al 2001[163]	Yes	Abstract. Trial 0560. Subgroup analysis NHP data
5	Cohen, Woolley et al 2001[164]	Yes	Abstract. Trial 0180. HAQ component parts
6	Jiang et al 2000[158]	Yes	FP. Trial 0560. Genant sharp scores vs Larsens scores
7	Cohen, Moreland 2001[105]	Yes	Abstract. Trial 0145.
8	Bresnihan et al 1998[102]	Yes	FP. Trial 0560
9	Cohen, Hurd et al 2002[104]	Yes	FP. Trial 0180
10	Fleishman, Tesser et al[106]	Yes	Abstract. Trial 0757. Safety study
11	Emery, Wolley et al 2001[165]	No	Abstract. Data duplication
12	Miller et al 2001[166]	No	Abstract. Combined analysis of 2 separate trials
13	Cravets et al 2001[167]	No	Abstract. Post-hoc analysis of Larsen scores from trial 0560 using imputed data from bootstrapping
14	Bresnihan 2001[26]	No	FP. Review
15	Bresnihan 1999[168]	No	FP. Review
16	Bresnihan 1996[169]	No	Abstract. Data duplication
17	Bresnihan 2001[170]	No	FP. Review
18	Campion et al 1996[171]	No	FP. No comparator arm
19	Cunnane et al 2001[172]	No	FP. Not an RCT, endpoints not appropriate
20	Snaith 2002[173]	No	Abstract. Open label extension, insufficient details to identify study
21	Cohen, Hurd et al 1999[174]	No	Abstract. Data duplication from trial 0180
22	Cunnane et al 1996[175]	No	Abstract. Data duplication. Subgroup analysis, endpoint not appropriate
23	Cunnane et al 1998[176]	No	Abstract. Data duplication. Subgroup analysis, endpoint not appropriate
24	Dayer, Bresnihan 2002[177]	No	FP. Review
25	Jiang et al 2001[178]	No	Abstract. Data duplication
26	Jiang et al 1998[179]	No	Abstract. Data duplication
27	Genant 2001[180]	No	FP. Data duplication
28	Lebsack et al 1992[97]	No	Abstract. Pharmacokinetic study
29	Nuki et al 1997[181]	No	Abstract. Non comparative extension of trial 0560
30	Schiff 2000[182]	No	FP. Review
31	Watt, Cobby 2001[183]	No	FP. Duplicate data

Citation		Inclusion?	Publication type and reason for exclusion / comment
32	Drevlow et al 1996[184]	No	FP.IL-1 receptor type 1, not anakinra
33	Bresnihan, Newmark et al 2000[185]	No	Abstract. Non comparative extension of trial 0560 & duplicate data
34	Bresnihan, Chan et al 2001[186]	No	Abstract. Duplicate data, & data on non comparative extension of trial 0560
35	Caldwell et al 2001[187]	No	Abstract. All treatment arms contained anakinra
36	Cohen, Nakelsky et al 2001[188]	No	Abstract. Not an RCT
37	Nuki, Bresnihan et al 2001[189]	No	Abstract. Non comparative extension of trial 0560
38	Schiff et al 2001[190]	No	Abstract. No comparator treatment arm
39	Genant et al 2000[191]	No	Abstract. Duplicate data, & data on non comparative extension of trial 0560
40	Wallis et al 2002[192]	No	Abstract. Review
41	Wallis et al 2002[193]	No	Abstract. Review & duplicate data
42	Yang et al 2002[194]	No	Abstract. Pharmacokinetic study
43	Hochberg et al 2002[131]	No	Abstract. Cost-minimisation study
44	Brennan et al 2002[132]	No	Abstract. Preliminary economic evaluation
45	Fleischmann et al 2002[195]	Yes	Abstract. Subgroup analysis of trial 0757
46	Fleischmann et al 2002[196]	No	Abstract. Duplicate data trial 0757
47	Schiff et al 2002[197]	No	Abstract. Sub-group analysis & duplicate data for trial 0757
48	Tesser et al 2002[198]	Yes	Abstract. Subgroup analysis of trial 0757
49	Fleischmann 2002[199]	No	Abstract. Duplicate data trial 0757
50	Rooney et al 2002[200]	No	Abstract. Duplicate data
51	Caldwell et al 2002[201]	No	Abstract. Duplicate data
52	Edwards et al 2002[202]	No	Abstract. No control arm
53	Andrias et al 2002[203]	No	Abstract. Juvenile RA
54	Schiff et al 2002[204]	No	Abstract. Duplicate data
55	Hochberg et al 2002[205]	No	Abstract. Review
56	Shergy et al 2002[206]	Yes	Abstract. Trial 0145 one year endpoint data
57	Shergy et al 2002[112]	No	Abstract. Duplicate data. Trial 0145 one year endpoint data
58	Cohen et al 2002[207]	No	Abstract. Duplicate data

Appendix 7: Scoring Using Modified Drummond Checklist for Amgen Economic Evaluation

Study design	
(1) The research question is stated	***Yes***
(2) The economic importance of the research question is stated	***Unclear***
(3) The viewpoint(s) of the analysis are clearly stated and justified	***Yes***
(4) The rationale for choosing the alternative programmes or interventions compared is stated	***Stated yes, but of questionable appropriateness***
(5) The alternatives being compared are clearly described	***Yes***
(6) The form of economic evaluation used is stated	***Yes***
(7) The choice of form of economic evaluation is justified in relation to the questions addressed	***Yes***
Data collection	
(8) The source(s) of effectiveness estimates used are stated	***Yes***
(9) Details of the design and results of effectiveness study are given (if based on a single study)	***Yes***
(10) Details of the method of synthesis or meta-analysis of estimates are given (if based on an overview of a number of effectiveness studies)	***Yes***
(11) The primary outcome measure(s) for the economic evaluation are clearly stated	***Yes***
(12) Methods to value health states and other benefits are stated	***Yes***
(13) Details of the subjects from whom valuations were obtained are given	***Yes***
(14) Productivity changes (if included) are reported separately	***N/A because of perspective***
(15) The relevance of productivity changes to the study question is discussed	***N/A***
(16) Quantities of resources are reported separately from their unit costs	***Unclear***
(17) Methods for the estimation of quantities and unit costs are described	***Yes***
(18) Currency and price data are recorded	***Yes***
(19) Details of currency of price adjustments for inflation or currency conversion are given	***N/A***
(20) Details of any model used are given	***Yes***
(21) The choice of model used and the key parameters on which it is based are justified	***Authors outline their reasons but we think these are not justified (see text)***
Analysis and interpretation of results	
(22) Time horizon of costs and benefits is stated	***Yes***
(23) The discount rate(s) is stated	***Yes***
(24) The choice of rate(s) is justified	***Determined by NICE Guidance***
(25) An explanation is given if costs or benefits are not discounted	***N/A***
(26) Details of statistical tests and confidence intervals are given for stochastic data	***NO! Transition probabilities are best estimates with no sampling variability explored.***
(27) The approach to sensitivity analysis is given	***Yes***
(28) The choice of variables for sensitivity analysis is justified	***No (see 26)***
(29) The ranges over which the variables are varied are stated	***Yes***
(30) Relevant alternatives are compared	***Only if interpreted as a last resort treatment***
(31) Incremental analysis is reported	***Yes***
(32) Major outcomes are presented in a disaggregated as well as aggregated form	***N/A, as model***
(33) The answer to the study question is given	***Yes***
(34) Conclusions follow from the data reported	***Not in our opinion***
(35) Conclusions are accompanied by the appropriate caveats	***Partially***

Appendix 8: Base Case ICER Calculations

Results with Anakinra "in the middle"

Strategy 1A with etanercept(4,000,000 patients used)

	Cost (£)	Q.S.E. (£)	QALYs	Q.S.E.	% Pall
with Ana	26088	6.5	5.119	0.0022	48.1
no Ana	16611	4.4	5.103	0.0021	53.0
difference	9477	7.8	0.016	0.0030	

ICER (£/QALY): 604 000 (436 000 – 985 000)

Strategy 1B without etanercept (2,000,000 patients)

	Cost (£)	Q.S.E. (£)	QALYs	Q.S.E.	% Pall
with Ana	27075	9.2	6.178	0.0033	52.5
no Ana	17429	6.3	6.153	0.0033	57.3
difference	9647	11.1	0.025	0.0046	

ICER (£/QALY): 379 000 (278 000 – 597 000)

Strategy 2A with etanercept

	Cost (£)	Q.S.E. (£)	QALYs	Q.S.E.	% Pall
with Ana	23498	13.1	4.109	0.0038	54.5
no Ana	13859	9.2	4.084	0.0038	60.6
difference	9639	16.0	0.025	0.0054	

ICER (£/QALY): 385 000 (270 000 – 674 000)

Strategy 2B without etanercept

	Cost (£)	Q.S.E. (£)	QALYs	Q.S.E.	% Pall
with Ana	24353	13.3	4.947	0.0042	58.2
no Ana	14510	9.4	4.912	0.0041	64.0
difference	9843	16.3	0.035	0.0059	

ICER (£/QALY): 278 000 (209 000 – 415 000)

Results with Anakinra last

Strategy 1A with etanercept (200,000 patients)

	Cost (£)	Q.S.E. (£)	QALYs	Q.S.E.	% Pall
with Ana	14171	24.0	3.149	0.0075	90.3
no Ana	2662	3.4	3.061	0.0075	100
difference	11508	24.3	0.088	0.0106	

ICER (£/QALY): 131 000 (106 000 – 173 000)

Strategy 1B without etanercept (400,000 patients)

	Cost (£)	Q.S.E. (£)	QALYs	Q.S.E.	% Pall
with Ana	14523	17.2	3.840	0.0058	91.6
no Ana	2841	2.5	3.729	0.0058	100
difference	11682	17.3	0.111	0.0082	

ICER (£/QALY): 105 000 (92 000 – 124 000)

Strategy 2A with etanercept (200,000 patients)

	Cost (£)	Q.S.E. (£)	QALYs	Q.S.E.	% Pall
with Ana	14021	23.8	2.844	0.0071	89.8
no Ana	2581	3.4	2.739	0.0071	100
difference	11441	24.1	0.105	0.0100	

ICER (£/QALY): 109 000 (91 000 – 134 000)

Strategy 2B without etanercept (200,000 patients)

	Cost (£)	Q.S.E. (£)	QALYs	Q.S.E.	% Pall
with Ana	14293	24.1	3.447	0.0078	91.2
no Ana	2742	3.5	3.337	0.0077	100
difference	11551	24.3	0.109	0.0110	

ICER (£/QALY): 106 000 (88 000 – 132 000)

Appendix 9 : Senstivity analyses

1. Time on anakinra

The time on anakinra was based on a single time-point. As an alternative to the exponential distribution, we tried the lowest value (0.62) of the shape parameter *a* for any of the DMARDs in Table 15, page 74. (This is the most favourable to anakinra.) To fit 23 % withdrawal at 24 weeks requires $b = 4.02$. The mean of the new distribution is 5.80 years, compared to 1.77 years in the base case.

Results with Anakinra "in the middle"

Strategy 1A with etanercept

	Cost (£)	Q.S.E. (£)	QALYs	Q.S.E.	% Pall
with Ana	34785	23.5	5.160	0.0043	40.9
no Ana	16613	8.7	5.100	0.0043	53.0
difference	18172	25.1	0.060	0.0061	

ICER (£/QALY): 301 000 (250 000 – 377 000)

Strategy 1B without etanercept

	Cost (£)	Q.S.E. (£)	QALYs	Q.S.E.	% Pall
with Ana	36317	24.0	6.228	0.0047	45.3
no Ana	17429	8.8	6.151	0.0046	57.3
difference	18887	25.6	0.077	0.0066	

ICER (£/QALY): 245 000 (209 000 – 295 000)

Strategy 2A with etanercept

	Cost (£)	Q.S.E. (£)	QALYs	Q.S.E.	% Pall
with Ana	32044	23.4	4.176	0.0039	46.2
no Ana	13859	9.2	4.084	0.0038	60.6
difference	18185	25.1	0.092	0.0054	

ICER (£/QALY): 198 000 (177 000 – 225 000)

Strategy 2B without etanercept

	Cost (£)	Q.S.E. (£)	QALYs	Q.S.E.	% Pall
with Ana	33423	24.0	5.021	0.0042	50.0
no Ana	14510	9.4	4.912	0.0041	64.0
difference	18913	25.7	0.109	0.0059	

ICER (£/QALY): 174 000 (157 000 – 195 000)

Results with anakinra last

Strategy 1A with etanercept

	Cost (£)	Q.S.E. (£)	QALYs	Q.S.E.	% Pall
with Ana	24254	75.5	3.316	0.0108	77.0
no Ana	2666	4.8	3.055	0.0105	100
difference	21588	75.6	0.261	0.0151	

ICER (£/QALY): 83 000 (74 000 – 94 000)

Strategy 1B without etanercept

	Cost (£)	Q.S.E. (£)	QALYs	Q.S.E.	% Pall
with Ana	25086	77.5	4.002	0.0119	79.1
no Ana	2844	4.9	3.741	0.0116	100
difference	22243	77.7	0.261	0.0166	

ICER (£/QALY): 85 000 (76 000 – 98 000)

Strategy 2A with etanercept

	Cost (£)	Q.S.E. (£)	QALYs	Q.S.E.	% Pall
with Ana	23725	73.9	2.967	0.0102	76.0
no Ana	2577	4.8	2.729	0.0100	100
difference	21148	74.0	0.238	0.0143	

ICER (£/QALY): 89 000 (79 000 – 101 000)

Strategy 2B without etanercept

	Cost (£)	Q.S.E. (£)	QALYs	Q.S.E.	% Pall
with Ana	24635	76.3	3.600	0.0112	78.2
no Ana	2736	4.9	3.328	0.0109	100
difference	21899	76.5	0.272	0.0156	

ICER (£/QALY): 81 000 (72 000 – 91 000)

2. Start and end effects

In this analysis the one-off loss of QALYs at start and end of DMARDs was omitted.

Results with Anakinra "in the middle"

Strategy 1A with etanercept

	Cost (£)	Q.S.E. (£)	QALYs	Q.S.E.	% Pall
with Ana	26092	13.0	5.235	0.0043	48.1
no Ana	16613	8.7	5.200	0.0043	53.0
difference	9479	15.6	0.034	0.0061	

ICER (£/QALY): 277 000 (205 000 – 431 000)

Strategy 1B without etanercept

	Cost (£)	Q.S.E. (£)	QALYs	Q.S.E.	% Pall
with Ana	27071	13.0	6.303	0.0047	52.6
no Ana	17429	8.8	6.254	0.0046	57.3
difference	9641	15.7	0.049	0.0066	

ICER (£/QALY): 199 000 (156 000 – 272 000)

Strategy 2A with etanercept

	Cost (£)	Q.S.E. (£)	QALYs	Q.S.E.	% Pall
with Ana	23498	13.1	4.200	0.0038	54.5
no Ana	13859	9.2	4.152	0.0038	60.6
difference	9639	16.0	0.048	0.0054	

ICER (£/QALY): 201 000 (164 000 – 258 000)

Strategy 2B without etanercept

	Cost (£)	Q.S.E. (£)	QALYs	Q.S.E.	% Pall
with Ana	24353	13.3	5.041	0.0042	58.3
no Ana	14510	9.4	4.981	0.0041	64.0
difference	9843	16.3	0.059	0.0059	

ICER (£/QALY): 166 000 (138 000 – 206 000)

Results with anakinra last

Strategy 1A with etanercept (200,000 patients)

	Cost (£)	Q.S.E. (£)	QALYs	Q.S.E.	% Pall
with Ana	14171	24.0	3.180	0.0075	90.3
no Ana	2662	3.4	3.061	0.0075	100
difference	11508	24.3	0.119	0.0106	

ICER (£/QALY): 97 000 (82 000 – 118 000)

Strategy 1B without etanercept (200,000 patients)

	Cost (£)	Q.S.E. (£)	QALYs	Q.S.E.	% Pall
with Ana	14515	24.3	3.857	0.0082	91.6
no Ana	2838	3.5	3.725	0.0082	100
difference	11677	24.5	0.132	0.0116	

ICER (£/QALY): 88 000 (75 000 – 107 000)

Strategy 2A with etanercept (200,000 patients)

	Cost (£)	Q.S.E. (£)	QALYs	Q.S.E.	% Pall
with Ana	14021	23.8	2.874	0.0071	89.8
no Ana	2581	3.4	2.739	0.0071	100
difference	11441	24.1	0.136	0.0100	

ICER (£/QALY): 84 000 (73 000 – 99 000)

Strategy 2B without etanercept (200,000 patients)

	Cost (£)	Q.S.E. (£)	QALYs	Q.S.E.	% Pall
with Ana	14293	24.1	3.478	0.0078	91.2
no Ana	2742	3.5	3.337	0.0077	100
difference	11551	24.3	0.140	0.0110	

ICER (£/QALY): 82 000 (71 000 – 98 000)

3. Effectiveness of anakinra

To see the effect of the benefit of anakinra on HAQ scores, we changed the HAQ improvement due to anakinra from 0.25 to 0.5. It is emphasised that there is no evidence to support this value: this is purely a "what if" analysis.

Results with Anakinra "in the middle"

Strategy 1A with etanercept

	Cost (£)	Q.S.E. (£)	QALYs	Q.S.E.	% Pall
with Ana	26181	12.9	5.224	0.0043	48.2
no Ana	16613	8.7	5.100	0.0043	53.0
difference	9568	15.6	0.124	0.0061	

ICER (£/QALY): 77 000 (70 000 – 88 000)

Strategy 1B without etanercept

	Cost (£)	Q.S.E. (£)	QALYs	Q.S.E.	% Pall
with Ana	27154	13.0	6.286	0.0047	52.7
no Ana	17429	8.8	6.151	0.0046	57.3
difference	9724	15.7	0.135	0.0066	

ICER (£/QALY): 72 000 (66 000 – 80 000)

Strategy 2A with etanercept

	Cost (£)	Q.S.E. (£)	QALYs	Q.S.E.	% Pall
with Ana	23597	13.1	4.220	0.0038	54.7
no Ana	13859	9.2	4.084	0.0038	60.6
difference	9738	16.0	0.136	0.0054	

ICER (£/QALY): 72 000 (67 000 – 78 000)

Strategy 2B without etanercept

	Cost (£)	Q.S.E. (£)	QALYs	Q.S.E.	% Pall
with Ana	24437	13.3	5.057	0.0042	58.5
no Ana	14510	9.4	4.912	0.0041	64.0
difference	9928	16.3	0.145	0.0059	

ICER (£/QALY): 68 000 (63 000 – 74 000)

Results with anakinra last

Strategy with etanercept (200,000 patients)

	Cost (£)	Q.S.E. (£)	QALYs	Q.S.E.	% Pall
with Ana	14244	24.1	3.258	0.0075	90.9
no Ana	2662	3.4	3.061	0.0075	100
difference	11581	24.4	0.197	0.0106	

ICER (£/QALY): 59 000 (53 000 – 66 000)

Strategy 1B without etanercept

	Cost (£)	Q.S.E. (£)	QALYs	Q.S.E.	% Pall
with Ana	14531	34.2	3.930	0.0116	92.1
no Ana	2844	4.9	3.741	0.0116	100
difference	11687	34.6	0.188	0.0164	

ICER (£/QALY): 62 000 (53 000 – 75 000)

Strategy 2A with etanercept (200,000 patients)

	Cost (£)	Q.S.E. (£)	QALYs	Q.S.E.	% Pall
with Ana	14095	23.9	2.950	0.0071	90.3
no Ana	2581	3.4	2.739	0.0071	100
difference	11514	24.2	0.212	0.0100	

ICER (£/QALY): 54 000 (50 000 – 60 000)

Strategy 2B without etanercept (400,000 patients)

	Cost (£)	Q.S.E. (£)	QALYs	Q.S.E.	% Pall
with Ana	14369	17.1	3.545	0.0055	91.6
no Ana	2745	2.4	3.340	0.0055	100
difference	11625	17.3	0.206	0.0078	

ICER (£/QALY): 57 000 (53 000 – 61 000)

4. Best case for anakinra

Results with Anakinra "in the middle"

Strategy 1A with etanercept

	Cost (£)	Q.S.E. (£)	QALYs	Q.S.E.	% Pall
with Ana	35071	23.6	5.573	0.0044	41.1
no Ana	16613	8.7	5.200	0.0043	53.0
difference	18459	25.2	0.372	0.0062	

ICER (£/QALY): 49 600 (48 000 – 51 300)

Strategy 1B without etanercept

	Cost (£)	Q.S.E. (£)	QALYs	Q.S.E.	% Pall
with Ana	36580	24.1	6.652	0.0048	45.5
no Ana	17429	8.8	6.254	0.0046	57.3
difference	19150	25.7	0.398	0.0067	

ICER (£/QALY): 48 100 (46 600 – 49 800)

Strategy 2A with etanercept

	Cost (£)	Q.S.E. (£)	QALYs	Q.S.E.	% Pall
with Ana	32347	23.5	4.557	0.0040	46.4
no Ana	13859	9.2	4.152	0.0038	60.6
difference	18488	25.3	0.405	0.0055	

ICER (£/QALY): 45 700 (44 500 – 47 000)

Strategy 2B without etanercept

	Cost (£)	Q.S.E. (£)	QALYs	Q.S.E.	% Pall
with Ana	33693	24.1	5.412	0.0043	50.2
no Ana	14510	9.4	4.981	0.0041	64.0
difference	19183	25.9	0.430	0.0060	

ICER (£/QALY): 44 600 (43 400 – 45 800)

Results with anakinra last

Strategy 1A with etanercept

	Cost (£)	Q.S.E. (£)	QALYs	Q.S.E.	% Pall
with Ana	24506	76.2	3.631	0.0112	77.7
no Ana	2666	4.8	3.055	0.0105	100
difference	21840	76.3	0.576	0.0154	

ICER (£/QALY): 37 900 (36 000 – 40 000)

Strategy 1B without etanercept

	Cost (£)	Q.S.E. (£)	QALYs	Q.S.E.	% Pall
with Ana	25302	78.0	4.328	0.0122	79.7
no Ana	2844	4.9	3.741	0.0116	100
difference	22459	78.2	0.587	0.0168	

ICER (£/QALY): 38 300 (36 200 – 40 600)

Strategy 2A with etanercept

	Cost (£)	Q.S.E. (£)	QALYs	Q.S.E.	% Pall
with Ana	24048	74.8	3.287	0.0106	76.7
no Ana	2577	4.8	2.729	0.0100	100
difference	21470	74.9	0.558	0.0146	

ICER (£/QALY): 38 400 (36 500 – 40 600)

Strategy 2B without etanercept

	Cost (£)	Q.S.E. (£)	QALYs	Q.S.E.	% Pall
with Ana	24916	77.1	3.924	0.0115	78.8
no Ana	2736	4.9	3.328	0.0109	100
difference	22180	77.2	0.596	0.0159	

ICER (£/QALY): 37 200 (35 300 – 39 400)

Appendix 10: Therapeutic approaches being investigated in RA

A number of other therapeutic approaches in RA are currently being investigated many of these involve modulation of the cytokine network. These include receptor antagonists, soluble receptors and monoclonal antibodies to other cytokines eg IL-6 as well as the direct use of 'anti-inflammatory' cytokines eg IL-10 & IL-4, IL-11.[21;208-210]

Further developments around TNF blockade are being actively investigated; D2E7 (adalimumab) a fully humanised anti-TNFα monoclonal antibody and PEG sTNF-RI, a pegylated soluble p55 TNF receptor.[211] Adalimumab has been submitted for a product licence in both the US and Europe.[212]

Clinical trials of experimental IL-1Ra gene therapy in RA are also underway. The human IL-1Ra gene is transferred to synovium by retro-viral vector. Clinical benefits in patients with RA are yet to be evaluated [213]

A novel biologic agent for the treatment of RA, CTLA4Ig, which is the first of a new class of drugs the ‘co-stimulation blockers’ is in phase 3 trials. This drug blocks T-cell activation and pro-inflammatory cytokine release. It is hoped that this drug will be launched in 2004[214]

Other therapeutic targets being investigated are oral toleragen therapy, adhesion molecules, modulation of T cell activity, blockade of effector function, vaccination with T cell receptors, major histocompatibility complex antigens, autologous hematopoietic stem cell transplantation.[209]

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